FORM PTO-1390	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER

50179-081   *PCt*

U.S. APPLIC. NO. (if known, see 37 CFR 1.5)

09/555275

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU98/00998	November 27, 1998	November 27, 1997

TITLE OF INVENTION

METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

APPLICANT(S) FOR DO/EO/US

John David BENTLEY, Leah Jane COSGROVE, Maurice John FRENKEL, Thomas Peter John GARRETT, Lynne Jean LAWRENCE, Meizhen LOU, George Oscar LOVRECZ, Neil Moreton MCKERN, Peter Archibald TULLOCH (deceased), Colin Wesley WARD

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendment has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information.

International Search Report
International Preliminary Examination Report
Front page of published International application

U.S. APPLIC. NO. (if known, see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/555275	PCT/AU98/00998	50179-081

	CALCULATIONS	PTO USE ONLY

17. ☒ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):
Search Report has been prepared by the EPO or JPO $840.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00
No international preliminary examination fee paid to USPTO (37 CFR 1.482)
but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $690.00

Neither international preliminary examination fee (37 CFR 1.482) nor
international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)
and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00

	CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	Number Filed	Number Extra	Rate		
Total Claims	33 -20 =	13	x $18.00	$ 234.00	
Independent Claims	2 -3 =	0	x $78.00	$	
Multiple dependent claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,334.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1,334.00	
Processing fee of $130.00 for furnishing the English translation later than the ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 1,334.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 1,334.00	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 500417 in the amount of $ 1,334.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500417. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

McDERMOTT, WILL & EMERY
600 13th Street, N.W.
Washington, DC 20005-3096
(202) 756-8000
Facsimile (202) 756-8087

SIGNATURE	*Robert L. Price*
NAME	Robert L. Price
REGISTRATION NUMBER	22,685
DATE	May 26, 2000

BASED ON FORM PTO-1390 (Rev. 5-93)

Docket No.: 50179-081

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of　　　　　　　　　　:

John David BENTLEY, et al.　　　　　:

　　　　　　　　　　　　　　　　　　:

Serial No.:　　　　　　　　　　　　:　Group Art Unit:

　　　　　　　　　　　　　　　　　　:

Filed: May 26, 2000　　　　　　　　:　Examiner:

　　　　　　　　　　　　　　　　　　:

For:　　METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to examination of the above-referenced application, please amend the application as

follows:

IN THE CLAIMS:

Claim 4, line 1, please change "any one of claims 1 to 3" to --claim 1--.

Claim 5, line 1, please change "any one of claims 1 to 4" to --claim 1--.

Claim 6, line 1, please change "any one of claims 1 to 4" to --claim 1--.

Claim 7, line 1, please change "any one of claims 1 to 4" to --claim 1--.

Claim 11, line 1, please change "any one of claims 1 to 10" to --claim 1--.

Claim 13, line 1, please change "any one of claims 1 to 12" to --claim 1--.

Claim 14, line 1, please change "any one of claims 1 to 12" to --claim 1--.

1

Claim 16, line 1, please delete "or claim 15".

Claim 19, line 1, please change "any one of claims 1 to 18" to --claim 1--.

Claim 20, line 1, please change "any one of claims 1 to 18" to --claim 1--.

Claim 23, line 1, please delete "or claim 22".

Claim 24, line 1, please change "any one of claims 21 to 23" to --claim 21--.

Claim 27, line 1, please change "any one of claims 21 to 26" to --claim 21--.

Claim 28, line 1, please change "any one of claims 21 to 26" to --claim 21--.

Claim 29, lines 3 and 4, please change "any one of claims 1 to 29" to --claim 1--.

REMARKS

The above-referenced application is amended to delete the multiple dependency of claims 4-7, 11, 13-14, 16, 19-20, 23-24, and 27-29 to avoid the multiple dependent claim filing fee.

Respectfully submitted,

MCDERMOTT, WILL & EMERY

Robert L. Price
Registration No. 22,685

600 13th Street, N.W.
Washington, DC 20005-3096
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Date: May 26, 2000
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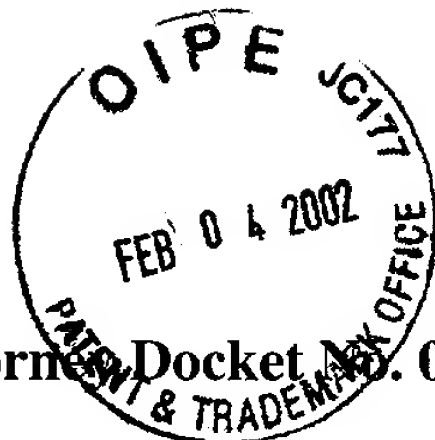
Attorney Docket No. 050179-0081   **PATENT APPLICATION**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of   )
)
John David BENTLEY, et al.   )
) Group Art Unit: TBA
Serial No.: 09/555,275   )
) Examiner: TBA
Filed: May 26, 2000   )
)
For: METHOD OF DESIGNING AGONISTS AND)
    ANTAGONISTS TO IGF RECEPTOR   )

RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATE/ELECTED OFFICE AND PRELIMINARY AMENDMENT

Honorable Assistant Commissioner for Patents
BOX SEQUENCE
Washington, D.C. 20231

Sir:

Prior to initial examination of the above-captioned patent application and in response to the Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office, mailed December 04, 2001, please amend the above-captioned patent application as follows:

IN THE SPECIFICATION:

Please substitute the second full paragraph on page 10 of the specification with the following rewritten paragraph.

-- **Figure 6.** Amino acid sequence of IGF-IR and related proteins (SEQ ID NO. 1, SEQ ID No. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, and SEQ ID NO. 6). a, L1 and L2

WDC99 554849-1.050179.0081

domains of human IGF-1R are shown based on a sequence alignment for the two proteins and a structural alignment for the L1 and L2 domains. Positions showing conservation physico-chemical properties of amino acids are boxed, residues used in the structural alignment are shown in Times Italic and residues which form the Trp 176 pocket are in Times Bold. Secondary structure elements for L1 (above the sequences) and L2 (below) are indicated as cylinders for helices and arrows for *B*-strands. Strands are shaded (pale, medium and dark grey) according to the *B*-sheet to which they belong. Disulfide bonds are also indicated. b, Cys-rich domains of human IGF-1R, IR and EGFR (domains 2 and 4) are aligned based on sequence and structural considerations. Secondary structural elements and disulfide bonds are indicated above the sequences. The dashed bond is only present in IR. Different types of disulfide bonded modules are labeled below the sequences as open, filled or broken lines. Boxed residues show conservation of physico-chemical properties and structurally conserved residues for modules 4-7 are shown in Times Italic. Residues from EGFR which do not conform to the pattern are in lowercase with probable disulfide bonding indicated below and the conserved Trp 176 and the semi-conserved Gln 182 are in Times Bold.--

Please substitute the second full paragraph on page 11 of the specification with the following rewritten paragraph.

-- **Figure 9**. Sequence alignment of hIGF-1R (SEQ ID NO.11), Hir (SEQ ID NO. 12), and hIRR (SEQ ID NO. 13) ectodomains, derived by use of the PileUp program in the software

package of Genetics Computer Group, 575 Science Drive, Madison, Wisconsin, USA. for

assignment of homologous 3D structrues see Figure 6.--

Please substitute the third paragraph on page 20 and continuing on to page 21 of the specification with the following rewritten paragraph.

-- The expression plasmid pEE14/IGF-1R/462 was constructed by inserting the

olignucleotide cassette (SEQ ID NO. 14 and SEQ ID NO. 15):

AatII

5' GACGTC GACGAT GACGATAAG GAACAAAAACTCATC

    D   V   D   D   D   D K   E   Q   K   L   I

          (EK cleavage)   (c-myc tail)

  S   E   E   D   L   N   (Stop)

TCAGAAGAGGATCTGAAT TAGAATTC GACGTC 3'

                        EcoRI AatII

encoding an enterokinase cleavage site, c-myc epitope tag (Hoogenboom, H.R., et a., 1991,

Nucleic acids Res. 19:4133-4137) and stop codon into the AatII site (within codon 462) of Igf-1r

cDNA in the mammalian expression vector pECE (Ebina, Y., et al., 1985, Cell, 40:747-758;

kindly supplied by W.J. Rutter, UCSF, USA), and introducing the DNA comprising the 5' 1521

bp of the cDNA (Ulrich, A., et al., 1986, EMBO J. 5:2503-2512) ligated to the oligonucleotide

cassette into the EcoRI site of the mammalian plasmid expression vector pEE14 (Bebbington, C.

R. & Hentschel, C. C. G., 1987, In: Glover, D. M., ed. DNA Cloning. Academic Press, San

Diego. Vol 3, p163; Celltech Ltd., UK). Plasmid pEE14/IGF-1R/462 was transfected into Lec8

mutant CHO cells (Stanley, P. 1989, Molec. Cellul. Biol. 9:377-383) obtained from the

American Tissue Culture Collection (CRL:1737), using Lipofectin (Gibco-BRL). Cell lines were

maintained after transfection in glutamine-free medium (Glascow modification of Eagle's

medium (GMEM; ICN Biomedicals, Australia) and 10% dialysed FCS (Sigma, Australia)

containing 25 μm methionine sulphoximine (MSX; Sigma, Australia) as described (Bebbington,

C.R. & Hentschel, C. C. G., 1987, In: Glover, D. M., ed. DNA Cloning. Academic Press, San

Diego. Vol3, p163). Transfectants were screened for protein expression by Western blotting and

sandwich enzyme-linked immunosorbent assay (ELISA) (Cosgrove, L., et a., 1995[,]) using

monoclonal antibody (Mab) 9E10 (Evan et al., 1985) as the capture antibody, and either

biotinylated anti-IGF-1R Mab 24-60 or 24-31 for detection (Soos et al., 1992; gifts from Ken

Siddle, University of Cambridge, UK). Large-scale cultivation of selected clones expressing

IGF-1R/462 was carried out in a Celligen Plus bioreactor (New Brunswick Scientific, USA)

containing 70 g Fibra-Cel Disks (Sterilin, UK) as carriers in a 1.25 L working volume.

Continuous perfusion culture using GMEM medium supplemented with non-essential amino

acids, nucleosides, 25μM MSX and 10% FCS was maintained for 1 to 2 weeks followed by the

more enriched DMEM/F12 without glutamine, with the same supplementation for the next 4-5

weeks. The fermentation production run was carried out three times under similar conditions,

and resulted in an estimated overall yield of 50 mg of receptor protein from 430 L of harvested

medium. Cell growth was poor during the initial stages of the fermentation when GMEM

medium was employed, but improved dramatically following the switch to the more enriched

medium. Target protein productivity was essentially constant during the period form ~100 to 700 h of the 760 h fermentation, as measured by ELISA using Mab 9E10 as capture antibody and bitinylated Mab 24-31 as the developing antibody.--

Please insert after page 46 and before the claims the attached paper copy of the Sequence Listing.

REMARKS

The specification is corrected and an initial Sequence Listing is herein submitted to comply with the requirements for an application containing a nucleotide and/or amino acid sequence.

Hereto is an attached substitute Sequence Listing in paper and computer readable format. The paper copy and computer readable copy of the substitute Sequence Listing are the same. The substitute Sequence Listing does not include new matter.

CONCLUSION

Entry of the Sequence Listing and favorable consideration are respectfully requested.

To the extent necessary, please grant any extension of time deemed necessary for entry of this communication. Please charge any deficient fees, or credit any overpayment of fees, to

Deposit Account 500417.

Respectfully submitted,

McDermott, Will & Emery

Kelli N Watson (signature)

Kelli N. Watson
Registration No. 47,170

DATE: February 4, 2002

McDermott, Will & Emery
600 Thirteenth Street, N.W.
Washington, D.C. 20005-3096
(202) 756-8351 (Telephone, direct)
(202) 756-8087 (Facsimile)

Attachments:

Notification of Missing Requirements Under 35 U.S.C. 371
Paper Copy of Sequence Listing
Diskette Containing Computer Readable
Copy of Sequence Listing

ATTACHMENT

Version With Markings To Show Changes Made

IN THE SPECIFICATION

The second full paragraph on page 10 of the specification is substituted with the following rewritten paragraph in its place.

-- **Figure 6.** Amino acid sequence of IGF-IR and related proteins (SEQ ID NO. 1, SEQ ID No. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, and SEQ ID NO. 6). a, L1 and L2 domains of human IGF-1R are shown based on a sequence alignment for the two proteins and a structural alignment for the L1 and L2 domains. Positions showing conservation physico-chemical properties of amino acids are boxed, residues used in the structural alignment are shown in Times Italic and residues which form the Trp 176 pocket are in Times Bold. Secondary structure elements for L1 (above the sequences) and L2 (below) are indicated as cylinders for helices and arrows for *B*-strands. Strands are shaded (pale, medium and dark grey) according to the *B*-sheet to which they belong. Disulfide bonds are also indicated. b, Cys-rich domains of human IGF-1R, IR and EGFR (domains 2 and 4) are aligned based on sequence and structural considerations. Secondary structural elements and disulfide bonds are indicated above the sequences. The dashed bond is only present in IR. Different types of disulfide bonded modules are label[l]ed below the sequences as open, filled or broken lines. Boxed residues show conservation of physico-chemical properties and structurally conserved residues for modules 4-7

are shown in Times Italic. Residues from EGFR which do not conform to the pattern are in lowercase with probable disulfide bonding indicated below and the conserved Trp 176 and the semi-conserved Gln 182 are in Times Bold.--

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-- **Figure 9**[:]. Sequence alignment of hIGF-1R (SEQ ID NO.11), Hir (SEQ ID NO. 12), and hIRR (SEQ ID NO. 13) ectodomains, derived by use of the PileUp program in the software package of Genetics Computer Group, 575 Science Drive, Madison, Wisconsin, USA. for assignment of homologous 3D structrues see Figure 6.--

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-- _____The expression plasmid pEE14/IGF-1R/462 was constructed by inserting the olignucleotide cassette (SEQ ID NO. 14 and SEQ ID NO. 15):

AatII
5' GACGTC GACGAT GACGATAAG GAACAAAAACTCATC
     D   V   D   D   D   D   K   E   Q   K   L   I
         (EK cleavage)   (c-myc tail)
     S   E   E   D   L   N   (Stop)
TCAGAAGAGGATCTGAAT TAGAATTC GACGTC 3'
                EcoRI   AatII

encoding an enterokinase cleavage site, c-myc epitope tag (Hoogenboom, H.R., et a., 1991, Nucleic acids Res. 19:4133-4137) and stop codon into the AatII site (within codon 462) of Igf-1r cDNA in the mammalian expression vector pECE (Ebina, Y., et al., 1985, Cell, 40:747-758; kindly supplied by W.J. Rutter, UCSF, USA), and introducing the DNA comprising the 5' 1521 bp of the cDNA (Ulrich, A., et al., 1986, EMBO J. 5:2503-2512) ligated to the oligonucleotide cassette into the EcoRI site of the mammalian plasmid expression vector pEE14 (Bebbington, C. R. & Hentschel, C. C. G., 1987, In: Glover, D. M., ed. DNA Cloning. Academic Press, San Diego. Vol 3, p163; Celltech Ltd., UK). Plasmid pEE14/IGF-1R/462 was transfected into Lec8 mutant CHO cells (Stanley, P. 1989, Molec. Cellul. Biol. 9:377-383) obtained from the American Tissue Culture Collection (CRL:1737), using Lipofectin (Gibco-BRL). Cell lines were maintained after transfection in glutamine-free medium (Glascow modification of Eagle's medium (GMEM; ICN Biomedicals, Australia) and 10% dialysed FCS (Sigma, Australia) containing 25 µm methionine sulphoximine (MSX; Sigma, Australia) as described (Bebbington, C.R. & Hentschel, C. C. G., 1987, In: Glover, D. M., ed. DNA Cloning. Academic Press, San Diego. Vol3, p163). Transfectants were screened for protein expression by Western blotting and sandwich enzyme-linked immunosorbent assay (ELISA) (Cosgrove, L., et a., 1995[,]) using monoclonal antibody (Mab) 9E10 (Evan et al., 1985) as the capture antibody, and either biotinylated anti-IGF-1R Mab 24-60 or 24-31 for detection (Soos et al., 1992; gifts from Ken Siddle, University of Cambridge, UK). Large-scale cultivation of selected clones expressing IGF-1R/462 was carried out in a Celligen Plus bioreactor (New Brunswick Scientific, USA)

containing 70 g Fibra-Cel Disks (Sterilin, UK) as carriers in a 1.25 L working volume.

Continuous perfusion culture using GMEM medium supplemented with non-essential amino

acids, nucleosides, $25\mu M$ MSX and 10% FCS was maintained for 1 to 2 weeks followed by the

more enriched DMEM/F12 without glutamine, with the same supplementation for the next 4-5

weeks. The fermentation production run was carried out three times under similar conditions,

and resulted in an estimated overall yield of 50 mg of receptor protein from 430 L of harvested

medium. Cell growth was poor during the initial stages of the fermentation when GMEM

medium was employed, but improved dramatically following the switch to the more enriched

medium. Target protein productivity was essentially constant during the period form ~100 to

700 h of the 760 h fermentation, as measured by ELISA using Mab 9E10 as capture antibody and

bitinylated Mab 24-31 as the developing antibody.--

**A paper copy of the Sequence Listing is inserted after page 46 and before the claims
of the specification.**

METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

Field of the Invention

This invention relates to the field of receptor structure and receptor/ligand interactions. In particular it relates to the field of using
5   receptor structure to predict the structure of related receptors and to the use of the determined structures and predicted structures to select and screen for agonists and antagonists of the polypeptide ligands.

Background of the Invention

Insulin is the peptide hormone that regulates glucose uptake and
10   metabolism. The two types of diabetes mellitus are associated either with an inability to produce insulin because of destruction of the pancreatic islet cells (Homo-Delarche, F. & Boitard, C.,1996, Immunol. Today 10: 456-460) or with poor glucose metabolism resulting from either insulin resistance at the target tissues, or from inadequate insulin secretion by the islets or faulty liver
15   function (Taylor, S. I., et al., 1994, Diabetes, 43: 735-740).

Insulin-like growth factors-1 and 2 (IGF-1 and 2) are structurally related to insulin, but are more important in tissue growth and development than in metabolism. They are primarily produced in the liver in response to growth hormone, but are also produced in most other tissues, where they
20   function as paracrine/autocrine regulators. The IGFs are strong mitogens, and are involved in numerous physiological states and certain cancers (Baserga, R., 1996, TibTech 14: 150-152).

Epidermal growth factor (EGF) is a small polypeptide cytokine that is unrelated to the insulin/IGF family. It stimulates marked proliferation of
25   epithelial tissues, and is a member of a larger family of structurally-related cytokines, such as transforming growth factor α, amphiregulin, betacellulin, heparin-binding EGF and some viral gene products. Abnormal EGF family signalling is a characteristic of certain cancers (Soler, C. & Carpenter, G., 1994 In Nicola, N. (ed) Guidebook to Cytokines and Their receptors", Oxford
30   Univ. Press, Oxford, pp194-197; Walker, F. & Burgess, A. W., 1994, In Nicola, N. (ed) Guidebook to Cytokines and Their receptors", Oxford Univ. Press, Oxford, pp198-201).

Each of these growth factors mediates its biological actions through binding to the corresponding receptor. The IR, IGF-1R and the insulin
35   receptor-related receptor (IRR), for which the ligand is not known, are closely related to each other, and are referred to as the insulin receptor subfamily. A

large body of information is now available concerning the primary structure
of these insulin receptor subfamily members (Ebina, Y., et al., 1985 Cell 40:
747-758; Ullrich, A., et al., 1985, Nature 313: 756-761; Ullrich, A. et al.,
1986, EMBO J 5: 2503-2512; Shier, P. & Watt, V. M., 1989, J. Biol. Chem. 264:

5   14605-14608) and the identification of some of their functional domains (for
reviews see De Meyts, P. 1994, Diabetologia 37: 135-148; Lee, J. & Pilch, P.
F. 1994 Amer. J. Physiol. 266: C319-C334.; Schaffer, L. 1994, Eur. J. Biochem.
221: 1127-1132). IGF-1R, IR and IRR are members of the tyrosine kinase
receptor superfamily and are closely related to the epidermal growth factor

10   receptor (EGFR) subfamily, with which they share significant sequence
identity in the extracellular region as well as in the cytoplasmic kinase
domains (Ullrich, A. et al., 1984 Nature 309: 418-425; Ward, C. W. et al., 1995
Proteins: Structure Function & Genetics 22: 141-153). Both the insulin and
EGF receptor subfamilies have a similar arrangement of two homologous

15   domains (L1 and L2) separated by a cys-rich region of approximately 160
amino acids containing 22-24 cys residues (Bajaj, M., et al., 1987 Biochim.
Biophys. Acta 916: 220-226; Ward, C. W. et al., 1995 Proteins: Structure
Function & Genetics 22: 141-153). The C-terminal portion of the IGF-1R
ectodomain (residues 463 to 906) is comprised of four domains: a connecting

20   domain, two fibronectin type 3 (Fn3) repeats, and an insert domain (O'Bryan,
J. P., et al., 1991 Mol Cell Biol 11: 5016-5031). The C-terminal portion of the
EGFR ectodomain (residues 477-621) consists solely of a second cys-rich
region containing 20 cys residues (Ullrich, A. et al., 1984, Nature 309: 418-
425).

25   Little is known about the secondary, tertiary and quaternary structure
of the ectodomains of these receptor subfamilies. Unlike the members of the
EGFR subfamily which are transmembrane monomers which dimerise on
binding ligand, the IR subfamily members are homodimers, held together by
disulphide bonds. The extracellular region of the IR/IGF-1R/IRR monomers

30   contains an α-chain (~ 703 to 735 amino acid residues) and 192-196 residues
of the ß-chain. There is a ~23 residue transmembrane segment, followed by
the cytoplasmic portion (354 to 408 amino acids), which contains the
catalytic tyrosine kinase domain flanked by juxtamembrane and C-tail
regulatory regions and is responsible for mediating all receptor-specific

35   functions (White, M. F. & Kahn, C. R. 1994 J. Biol. Chem. 269: 1-4). Chemical
analyses of the receptor suggest that the α-chains are linked to the ß-chains

via a single disulphide bond, with the IR dimer being formed by at least two α-α disulphide linkages (Finn, F. M., et al., 1990, Proc. Natl. Acad. Sci. 87: 419-423; Chiacchia, K. B., 1991, Biochem. Biophys. Res. Commun. 176, 1178-1182; Schaffer, L. & Ljungqvist, L., 1992, Biochem. Biophys. Res. Comm. 189:
5   650-653; Sparrow, L. G., et al., 1997, J. Biol. Chem. 47: 29460-29467).

Although the three-dimensional (3D) structures of the ligands EGF, TGF-alpha (Hommel, U., et al., 1992, J. Mol. Biol. 227:271-282), insulin (Dodson, E. J., et al., 1983, Biopolymers 22:281-291), IGF-1 (Sato, A., et al., 1993, Int J Peptide Protein Res 41:433-440) and IGF-2 (Torres, A. M., et
10   al.,1995, J. Mol. Biol. 248:385-401) are known, and numerous analytical and functional studies of ligand binding to EGFR (Soler, C. & Carpenter, G., 1994 In Nicola (ed) Guidebook to Cytokines and Their receptors", Oxford Univ. Press, Oxford, pp194-197), IGF-1R and IR (see De Meyts, P., 1994 Diabetologia, 37:135-148) have been carried out, the mechanisms of ligand
15   binding and subsequent transmembrane signalling have not been resolved.

Ligand-induced, receptor-mediated phosphorylation is the signalling mechanism by which most cytokines, polypeptide hormones and membrane-anchored ligands exert their biological effects. The primary kinase may be part of the intracellular portion of the transmembrane receptor protein, as in
20   the tyrosine kinase receptors (for review see Yarden, Y., et al., 1988, Ann. Rev. Biochem. 57:443-478) or the Ser/Thr kinase receptors (Alevizopoulos, A. & Mermod, N., 1997, BioEssays, 19:581-591) or may be non-covalently associated with the cytoplasmic tail of the transmembrane protein(s) making up the receptor complex, as in the case of the haemopoietic growth factor
25   receptors (Stahl, N., et al., 1995, Science 267:1349-1353). The end result is the same, ligand binding leads to receptor dimerization or oligomerization or a conformational change in pre-existing receptor dimers or oligomers, resulting in activation by transphosphorylation, of the covalently attached or non-covalently associated protein kinase domains (Hunter, T., 1995, Cell,
30   80:225-236).

Many oncogenes have been shown to be homologous to growth factors, growth factor receptors or molecules in the signal transduction pathways (Baserga, R.,1994 Cell, 79:927-930; Hunter, T., 1997 Cell, 88:333-346). One of the best examples is v-Erb (related to the EGFR). Since
35   overexpression of a number of growth factor receptors results in ligand-dependent transformation, an alternate strategy for oncogenes is to regulate

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the expression of growth factor receptors or their ligands or to directly bind to the receptors to stimulate the same effect (Baserga, R., 1994 Cell, 79:927-930). Examples are v-Src, which activates IGF-1 R intracellularly; c-Myb, which transforms cells by enhancing the expression of IGF1R; and SV40 T antigen which interacts with the IGF-1R and enhances the secretion of IGF-1 (see Baserga, R.,1994 Cell, 79:927-930 for review). Cells in which the IGF-1R has been disrupted or deleted cannot be transformed by SV40 T antigen. If oncogenes activate growth factors and their receptors, then tumour suppressor genes should have the opposite effect. One good example of this is the Wilm's tumour suppressor gene, WT1, which suppresses the expression of IGF-1R (Drummond, J. A., et al., 1992, Science, 257:275-277). Cells that are driven to proliferate by oncogenes undergo massive apoptosis when growth factor receptors are ablated, since, unlike normal cells, they appear unable to withdraw from the cell-cycle and enter into the G_0 phase (Baserga, R.,1994 Cell, 79:927-930).

The insulin-like growth factor-1 receptor (IGF-1R) is one of several growth-factor receptors that regulate the proliferation of mammalian cells. However, its ubiquitousness and certain unique aspects of its function make IGF-1R an ideal target for specific therapeutic interventions against abnormal growth, with very little effect on normal cells (see Baserga, R., 1996 TIBTECH, 14:150-152). The receptor is activated by IGF1, IGF2 and insulin, and plays a major role in cellular proliferation in at least three ways: it is essential for optimal growth of cells *in vitro* and *in vivo*; several cell types require IGF-1R to maintain the transformed state; and activated IGF-1R has a protective effect against apoptotic cell death (Baserga, R., 1996 TIBTECH, 14:150-152). These properties alone make it an ideal target for therapeutic interventions. Transgenic experiments have shown that IGF-1R is not an absolute requirement for cell growth, but is essential for the establishment of the transformed state (Baserga, R.,1994 Cell, 79: 927-930). In several cases (human glioblastoma, human melanoma; human breast carcinoma: human lung carcinoma; human ovarian carcinoma; human rhabdomyosarcoma; mouse melanoma, mouse leukaemia; rat glioblastoma; rat rhabdomyosarcoma; hamster mesothelioma) the transformed phenotype can be reversed by decreasing the expression of IGF-1R using antisense to IGF-1R (Baserga, R., 1996 TIBTECH 14:150-152); or by interfering with its function by antibodies to IGF-1R (human breast carcinoma; human

rhabdomyosarcoma) or by dominant negatives of IGF-1R (rat glioblastoma; Baserga, R.,1996 TIBTECH 14:150-152).

Three effects are observed when the function of IGF-1R is impaired: tumour cells undergo massive apoptosis which results in inhibition of tumourogenesis; surviving tumour cells are eliminated by a specific immune response; and such a host response can cause a regression of an established wild-type tumour (Resnicoff, M., et al., 1995, Cancer Res. 54:2218-2222). These effects, plus the fact that interference with IGF-1R function has a limited effect on normal cells (partial inhibition of growth without apoptosis) makes IGF-1R a unique target for therapeutic interventions (Baserga, R., 1996 TIBTECH 14:150-152). In addition IGF-1R is downstream of many other growth factor receptors, which makes it an even more generalised target. The implication of these findings is that if the number of IGF-1Rs on cells can be decreased or their function antagonised, then tumours cease to grow and can be removed immunologically. These studies establish that IGF-1R antagonists will be extremely important therapeutically.

Many cancer cells have constitutively active EGFR (Sandgreen, E. P., et al., 1990, Cell, 61:1121-135; Karnes, W. E. J., et al., 1992, Gastroenterology, 102:474-485) or other EGFR family members (Hines, N. E.,1993, Semin. Cancer Biol. 4:19-26). Elevated levels of activated EGFR occur in bladder, breast, lung and brain tumours (Harris, A. L., et al., 1989, In Furth & Greaves (eds) The Molecular Diagnostics of human cancer. Cold Spring Harbor Lab. Press, CSH, NY, pp353-357). Antibodies to EGFR can inhibit ligand activation of EGFR (Sato, J. D., et al., 1983 Mol. Biol. Med. 1:511-529) and the growth of many epithelial cell lines (Aboud-Pirak E., et al., 1988, J. Natl Cancer Inst. 85:1327-1331). Patients receiving repeated doses of a humanised chimeric anti-EGFR monoclonal antibody showed signs of disease stabilization. The large doses required and the cost of production of humanised monoclonal antibody is likely to limit the application of this type of therapy. These findings indicate that the development of EGF antagonists will be attractive anticancer agents.

Summary of the Invention

The present inventors have now obtained 3D structural information concerning the insulin-like growth factor receptor (IGF-1R). This information can be used to predict the structure of related members of the insulin

receptor family and provides a rational basis for the development of ligands for specific therapeutic applications.

Accordingly, in a first aspect the present invention provides a method of designing a compound able to bind to a molecule of the insulin receptor family and to modulate an activity mediated by the molecule, including the step of assessing the stereochemical complementarity between the compound and the receptor site of the molecule, wherein the receptor site includes:

(a)   amino acids 1 to 462 of the receptor for IGF-1, having the atomic coordinates substantially as shown in Figure 1;

(b)   a subset of said amino acids, or;

(c)   amino acids present in the amino acid sequence of a member of the insulin receptor family, which form an equivalent three-dimensional structure to that of the receptor molecule as depicted in Figure 1.

The phrase "insulin receptor family" encompasses, for example, IGF-1R, IR and IRR. In general, insulin receptor family members show similar domain arrangements and share significant sequence identity (preferably at least 40% identity).

By "stereochemical complementarity" we mean that the biologically active substance or a portion thereof correlates, in the manner of the classic "lock-and-key" visualisation of ligand-receptor interaction, with the groove in the receptor site.

In a preferred embodiment of this aspect of the invention, the compound is selected or modified from a known compound identified from a database.

In a further preferred embodiment, the compound is designed so as to complement the structure of the receptor molecule as depicted in Figure 1.

In a further preferred embodiment, the compound has structural regions able to make close contact with amino acid residues at the surface of the receptor site lining the groove, as depicted in Figure 2.

In a further preferred embodiment, the compound has a stereochemistry such that it can interact with both the L1 and L2 domains of the receptor site.

In a further preferred embodiment, the compound has a stereochemistry such that it can interact with the L1 domain of a first monomer of the receptor homodimer, and with the L2 domain of the other monomer of the receptor homodimer.

In a further preferred embodiment, the interaction of the compound with the receptor site alters the position of at least one of the L1, L2 or cysteine-

rich domains of the receptor molecule relative to the position of at least one of the other of said domains. Preferably, the compound interacts with the β sheet of the L1 domain of the receptor molecule, thereby causing an alteration in the position of the L1 domain relative to the position of the cysteine-rich domain or

5 of the L2 domain. Alternatively, the compound interacts with the receptor site in the region of the interface between the L1 domain an the cysteine-rich domain of the receptor molecule, thereby causing the L1 domain and the cysteine-rich domain to move away from each other. In another preferred embodiment, the compound interacts with the hinge region between the L2 domain and the

10 cysteine-rich domain of the receptor molecule, thereby causing an alteration in the positions of the L2 domain and the cysteine-rich domain relative to each other.

In a further preferred embodiment, the stereochemical complementarity between the compound and the receptor site is such that the compound has a K_b

15 for the receptor side of less than 10^{-6}M, more preferably is less than 10^{-8}M.

In a further preferred embodiment or the first aspect of the present invention, the compound has the ability to increase an activity mediated by the receptor molecule.

In a further preferred embodiment, the compound has the ability to

20 decrease an activity mediated by the receptor molecule. Preferably, the stereochemical interaction between the compound and the receptor site is adapted to prevent the binding of a natural ligand of the receptor molecule to the receptor site. It is preferred that the compound has a K_i of less than 10^{-6}M, more preferably less than 10^{-8}M and more preferably less than 10^{-9}M.

25 In a further preferred embodiment of the first aspect of the present invention, the receptor is the IGF-1R, or the insulin receptor.

In a second aspect, the present invention provides a computer-assisted method for identifying potential compounds able to bind to a molecule of the insulin receptor family and to modulate an activity mediated by the molecule,

30 using a programmed computer including a processor, an input device, and an output device, including the steps of:

(a) inputting into the programmed computer, through the input device, data comprising the atomic coordinates of the IGF-1R molecule as shown in Figure 1, or a subset thereof;

35 (b) generating, using computer methods, a set of atomic coordinates of a structure that possesses stereochemical complementarity to the atomic

coordinates of the IGF-1R site as shown in Figure 1, or a subset thereof, thereby generating a criteria data set;

(c)   comparing, using the processor, the criteria data set to a computer database of chemical structures;

5   (d)   selecting from the database, using computer methods, chemical structures which are structurally similar to a portion of said criteria data set; and

(e)   outputting, to the output device, the selected chemical structures which are similar to a portion of the criteria data set.

In a preferred embodiment of the second aspect, the programmed
10   computer includes a data storage system which includes the dtatbase of chemical structures.

In a preferred embodiment of the second aspect, the method is used to identify potential compounds which have the ability to decrease an activity mediated by the receptor.

15   In another preferred embodiment, the computer-assisted method further includes the step of selecting one or more chemical structures from step (e) which interact with the receptor site of the molecule in a manner which prevents the binding of natural ligands to the receptor site.

In another preferred embodiment, the computer-assisted method further
20   includes the step of obtaining a compound with a chemical structure selected in steps (d) and (e), and testing the compound for the ability to decrease an activity mediated by the receptor.

In a further preferred embodiment, the computer-assisted method is used to identify potential compounds which have the ability to increase an
25   activity mediated by the receptor molecule.

In another preferred embodiment, the computer-assisted method further includes the step of obtaining a molecule with a chemical structure selected in steps (d) and (e), and testing the compound for the ability to increase an activity mediated by the receptor.

30   In a further preferred embodiment of the second aspect of the present invention, the receptor is the IGF-1R, or the insulin receptor.

In a third aspect, the present invention provides a method of screening of a putative compound having the ability to modulate the activity of a receptor of the insulin receptor family, including the steps of identifying a putative
35   compound by a method according to the first or second aspects, and testing the

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compound for the ability to increase or decrease an activity mediated by the receptor.

In a preferred embodiment of the third aspect, the test is carried out *in vitro*.

5   In a further preferred embodiment of the third aspect, the test is a high throughput assay.

In a preferred embodiment of the third aspect, the test is carried out *in vivo*.

10   **Brief Description of the Drawings**

Figure 1. IGF-1R residues 1-462, in terms of atomic coordinates refined to a resolution of 2.6 Å (average accuracy ≈ 0.3Å). The coordinates are in relation to a Cartesian system of orthogonal axes.

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Figure 2. Depiction of the residues lining the groove of the IGF-1R receptor fragment 1-462.

Figure 3. Gel filtration chromatography of affinity-purified IGF-1R/462
20   protein. The protein was purified on a Superdex S200 column (Pharmacia) fitted to a BioLogic L.C. system (Biorad), equilibrated and eluted at 0.8 ml/min with 40 mM Tris/150 mM NaCl/0.02% NaN3 adjusted to pH 8.0. (a) Protein eluting in peak 1 contained aggregated IGF-1R/462 protein, peak 2 contained monomeric protein and peak 3 contained the c-myc undecapeptide
25   used for elution from the Mab 9E10 immunoaffinity column. (b) Non-reduced SDS-PAGE of fraction 2 from IGF-1R/462 obtained following Superdex S200 (Fig.1a). Standard proteins are indicated.

Figure 4. Ion exchange chromatography of affinity-purified, truncated IGF-
30   1R ectodomain. A mixture of gradient and isocratic elution chromatography was performed on a Resource Q column (Pharmacia) fitted to a BioLogic System (Biorad), using 20 mM Tris/pH 8.0 as buffer A and the same buffer containing 1M NaCl as buffer B. Protein solution in TBSA was diluted at least 1:2 with water and loaded onto the column at 2 ml/min. Elution was
35   monitored by absorbance (280 nm) and conductivity (mS/cm). Target protein (peak 2) eluted isocratically with 20 mM Tris/0.14 M NaCl pH 8.0. Inset:

Isoelectric focusing gel (pH 3 - 7; Novex Australia Pty Ltd)of fraction 2. The pI was estimated at 5.1 from standard proteins (not shown).

Figure 5. Polypeptide fold for residues 1-462 of IGF-1R. The L1 domain is at
the top, viewed from the N-terminal end and L2 is at the bottom. The space
at the centre is of sufficient size to accommodate IGF-1. Helices are
indicated by curled ribbon and b-strands by arrows. Cysteine side chains are
drawn as ball-and-stick with lines showing disulfide bonds. The arrow
points in the direction of view for L1 in Figure 7.

Figure 6. Amino acid sequences of IGF-1R and related proteins. a, L1 and L2
domains of human IGF-1R and IR are shown based on a sequence alignment
for the two proteins and a structural alignment for the L1 and L2domains.
Positions showing conservation physico-chemical properties of amino acids
are boxed, residues used in the structural alignment are shown in Times
Italic and residues which form the Trp 176 pocket are in Times Bold.
Secondary structure elements for L1 (above the sequences) and L2 (below)
are indicated as cylinders for helices and arrows for β-strands. Strands are
shaded (pale, medium and dark grey) according to the β-sheet to which they
belong. Disulfide bonds are also indicated. b, Cys-rich domains of human
IGF-1R, IR and EGFR (domains 2 and 4) are aligned based on sequence and
structural considerations. Secondary structural elements and disulfide bonds
are indicated above the sequences. The dashed bond is only present in IR.
Different types of disulfide bonded modules are labelled below the sequences
as open, filled or broken lines. Boxed residues show conservation of physico-
chemical properties and structurally conserved residues for modules 4-7 are
shown in Times Italic. Residues from EGFR which do not conform to the
pattern are in lowercase with probable disulfide bonding indicated below and
the conserved Trp 176 and the semi-conserved Gln 182 are in Times Bold.

Figure 7. Stereo view of a superposition of the L1 (white) and L2 (black)
domains. Residues numbers above are for L1 and below for L2. The side
chain of Trp 176 which protrudes into the core of L1 is drawn as ball-and-
stick.

Figure 8. Schematic diagram showing the association of three β-finger motifs. β-strands are drawn as arrows and disulfide bonds as zigzags.

Figure 9: Sequence alignment of hIGF-1R, hIR and hIRR ectodomains,
5 derived by use of the PileUp program in the software package of the Genetics Computer Group, 575 Science Drive, Madison, Wisconsin, USA.
For assignment of homologous 3D structures see Figure 6.

Figure 10   Gel filtration chromatography of insulin receptor ectodomain
10 and MFab complexes. hIR -11 ectodomain dimer (5 - 20 mg) was complexed with MFab derivatives (15-25 mg each) of the anti-hIR antibodies 18-44, 83-7 and 83-14 (Soos et al., 1986). Flution profiles were generated from samples loaded on to a Superdex S200 column (Pharmacia), connected to a BioLogic chromatography system (Biorad) and monitored at 280 nm. The column was
15 eluted at 0.8 ml/min with 40 mM Tris/150 mM sodium chloride/0.02% sodium azide buffer adjusted to pH 8.0: Profile 0, hIR -11 ectodomain, Profile 1, ectodomain mixed with MFab 18-44; Profile 2 , ectodomain mixed with MFab18-44 and MFab 83-14; Profile 3, ectodomain mixed with MFab 18-44, MFab 83-14 and MFab 83-7. The apparent mass of each complex was
20 determined from a plot of the following standard proteins: thyroglobulin (660 kDa), ferritin (440 kDa), bovine gamma globulin (158 kDa), bovine serum albumin (67 kDa), chicken ovalbumin (44 kDa) and equine myoglobin (17 kDa).

25 **Figure 11** Schematic representations of electron microscopy images of the hIR ectodomain dimer.

Detailed Description of the Invention
        We describe herein the expression, purification, and crystallization of
30 a recombinant truncated IGF-1R fragment (residues 1-462) containing the L1-cysteine-rich-L2 region of the ectodomain. The selected truncation position is just downstream of the exon 6/exon 7 junction (Abbott. A. M., et al., 1992. J Biol Chem., 267:10759-10763), and occurs at a position where the sequences of the IR and EGFR families diverge markedly (Ward, C. W., et al.,1995,
35 Proteins: Struct., Funct., Genet. 22:141-153; Lax, I., et al., 1988, Molec. Cellul. Biol. 8:1970-1978) suggesting it represents a domain boundary. To

limit the effects of glycosylation, the IGF-1R fragment was expressed in Lec8 cells, a glycosylation mutant of Chinese hamster ovary (CHO) cells, whose defined glycosylation defect produces N-linked oligosaccharides truncated at N-acetyl glucosamine residues distal to mannose residues (Stanley, P. 1989,

5   Molec. Cellul. Biol. 9:377-383). Such an approach has facilitated glycoprotein crystallization (Davis, S. J., et al., 1993, Protein Eng. 6:229-232; Liu, J., et al., 1996, J. Biol. Chem. 271:33639-33646).

The IGF-1R construct described herein includes a c-myc peptide tag (Hoogenboom, H. R., et al.,1991, Nucleic Acids Res. 19:4133-4137) that is

10   recognised by the Mab 9E10 (Evan, G. I., et al., 1985, Mol. Cell. Biol. 5:3610-3616) enabling the expressed product to be purified by peptide elution from an antibody affinity column followed by gel filtration over Superdex S200. The purified proteins crystallized under a sparse matrix screen (Jancarik, J. & Kim, S.-H., 1991, J. Appl. Cryst. 24:409-411) but the crystals were of variable

15   quality, with the best diffracting to 3.0-3.5Å. Isocratic gradient elution by anion-exchange chromatography yielded protein that was less heterogenous and gave crystals of sufficient quality to determine the structure of the first three domains of the human IGF-1R.

The IGF-1R fragment consisted of residues 1-462 of IGF-1R linked via

20   an enterokinase-cleavable pentapeptide sequence to an eleven residue c-myc peptide tag at the C-terminal end. The fragment was expressed in Lec8 cells by continuous media perfusion in a bioreactor using porous carrier disks. It was secreted into the culture medium and purified by peptide elution from an anti-c-myc antibody column followed by Superdex S200 gel filtration. The

25   receptor fragment bound two anti-IGF-1R monoclonal antibodies, 24-31 and 24-60, which recognize conformational epitopes, but could not be shown to bind IGF-1 or IGF-2. Crystals of variable quality were grown as rhombic prisms in 1.7 M ammonium sulfate at pH 7.5 with the best diffracting to 3.0-3.5 Å. Further purification by isocratic elution on an anion-exchange column

30   gave protein which produced better quality crystals, diffracting to 2.6 Å, that were suitable for X-ray structure determination.

The structure of this fragment (IGF-1R residues 1-462; L1-cys rich-L2 domains) has been determined to 2.6 Å resolution by X-ray diffraction. The L domains each adopt a compact shape consisting of a single stranded right-

35   handed β-helix. The cys-rich region is composed of eight disulphide-bonded modules, seven of which form a rod-shaped domain with modules associated

in a novel manner. At the centre of this reasonably extended structure is a space, bounded by all three domains, and of sufficient size to accommodate a ligand molecule. Functional studies on IGF-1R and other members of the insulin receptor family show that the regions primarily responsible for
5   hormone-binding map to this central site. Thus this structure gives a first view of how members of the insulin receptor family might interact with their ligands.

Another group has reported the crystallization of a related receptor, the EGFR, in a complex with its ligand EGF (Weber, W., et al., 1994, J
10   Chromat. 679:181-189). However, difficulties were encountered with these crystals which diffracted to only 6 Å, insufficient for the determination of an atomic resolution structure of this complex (Weber, W., et al., 1994, J Chromat 679:181-189) or the generation of accurate models of structurally related receptor domains such as IGF-1R and IR by homology modelling.
15   The present inventors have developed 3D structural information about cytokine receptors in order to enable a more accurate understanding of how the binding of ligand leads to signal transduction. Such information provides a rational basis for the development of ligands for specific therapeutic applications, something that heretofore could not have been
20   predicted *de novo* from available sequence data.

The precise mechanisms underlying the binding of agonists and antagonists to the IGF-1R site are not fully clarified. However, the binding of ligands to the receptor site, preferably with an affinity in the order of 10^{-8}M or higher, is understood to arise from enhanced stereochemical
25   complementarity relative to naturally occurring IGF-1 ligands.

Such stereochemical complementarity, pursuant to the present invention, is characteristic of a molecule that matches intra-site surface residues lining the groove of the receptor site as eneumerated by the coordinates set out in Figure 1. The residues lining the groove are depicted
30   in Figure 2. By "match" we mean that the identified portions interact with the surface residues, for example, via hydrogen bonding or by enthalpy-reducing Van der Waals interactions which promote desolvation of the biologically active substance within the site, in such a way that retention of the biologically active substance within the groove is favoured energetically.
35   Substances which are complemetary to the shape of the receptor site characterised by amino acids positioned at atomic coordinates set out in

Figure 1 may be able to bind to the receptor site and, when the binding is sufficiently strong, substantially prohibit binding of the naturally occurring ligands to the site.

It will be appreciated that it is not necessary that the complementarity between ligands and the receptor site extend over all residues lining the groove in order to inhibit binding of the natural ligand. Accordingly, agonists or antagonists which bind to a portion of the residues lining the groove are encompassed by the present invention.

In general, the design of a molecule possessing stereochemical complementarity can be accomplished by means of techniques that optimize, either chemically or geometrically, the "fit" between a molecule and a target receptor. Known techniques of this sort are reviewed by Sheridan and Venkataraghavan, Acc. Chem Res. 1987 20 322; Goodford, J. Med. Chem. 1984 27 557; Beddell, Chem. Soc. Reviews 1985, 279; Hol, Angew. Chem. 1986 25 767 and Verlinde C.L.M.J & Hol, W.G.J. Structure 1994, 2, 577, the respective contents of which are hereby incorporated by reference. See also Blundell et al., Nature 1987 326 347 (drug development based on information regarding receptor structure).

Thus, there are two preferred approaches to designing a molecule, according to the present invention, that complements the shape of IGF-1R or a related receptor molecule. By the geometric approach, the number of internal degrees of freedom (and the corresponding local minima in the molecular conformation space) is reduced by considering only the geometric (hard-sphere) interactions of two rigid bodies, where one body (the active site) contains "pockets" or "grooves" that form binding sites for the second body (the complementing molecule, as ligand). The second preferred approach entails an assessment of the interaction of respective chemical groups ("probes") with the active site at sample positions within and around the site, resulting in an array of energy values from which three-dimensional contour surfaces at selected energy levels can be generated.

The geometric approach is illustrated by Kuntz et al., J. Mol. Biol. 1982 161 269, the contents of which are hereby incorporated by reference, whose algorithm for ligand design is implemented in a commercial software package distributed by the Regents of the University of California and further described in a document, provided by the distributor, which is entitled "Overview of the DOCK Package, Version 1.0,", the contents of which are

hereby incorporated by reference. Pursuant to the Kuntz algorithm, the shape of the cavity represented by the IGF-R1 site is defined as a series of overlapping spheres of different radii. One or more extant data bases of crystallographic data, such as the Cambridge Structural Database System

5   maintained by Cambridge University (University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.) and the Protein Data Bank maintained by Brookhaven National Laboratory (Chemistry Dept. Upton, NY 11973, U.S.A.), is then searched for molecules which approximate the shape thus defined.

10   Molecules identified in this way, on the basis of geometric parameters, can then be modified to satisfy criteria associated with chemical complementarity, such as hydrogen bonding, ionic interactions and Van der Waals interactions.

          The chemical-probe approach to ligand design is described, for

15   example, by Goodford, J. Med. Chem. 1985 <u>28</u> 849, the contents of which are hereby incorporated by reference, and is implemented in several commercial software packages, such as GRID (product of Molecular Discovery Ltd., West Way House, Elms Parade, Oxford OX2 9LL, U.K.). Pursuant to this approach, the chemical prerequisites for a site-complementing molecule are identified

20   at the outset, by probing the active site (as represented via the atomic coordinates shown in Fig. 1) with different chemical probes, e.g., water, a methyl group, an amine nitrogen, a carboxyl oxygen, and a hydroxyl. Favored sites for interaction between the active site and each probe are thus determined, and from the resulting three-dimensional pattern of such sites a

25   putative complementary molecule can be generated.

          The chemical-probe approach is especially useful in defining variants of a molecule known to bind the target receptor. Accordingly, crystallographic analysis of IGF-1 bound to the receptor site is expected to provide useful information regarding the interaction between the archetype

30   ligand and the active site of interest.

          Programs suitable for searching three-dimensional databases to identify molecules bearing a desired pharmacophore include: MACCS-3D and ISIS/3D (Molecular Design Ltd., San Leandro, CA), ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.), and Sybyl/3DB Unity (Tripos Associates, St.

35   Louis, MO).

Programs suitable for pharmacophore selection and design include: DISCO (Abbott Laboratories, Abbott Park, IL), Catalyst (Bio-CAD Corp., Mountain View, CA), and ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.).

5   Databases of chemical structures are available from a number of sources including Cambridge Crystallographic Data Centre (Cambridge, U.K.) and Chemical Abstracts Service (Columbus, OH).

De novo design programs include Ludi (Biosym Technologies Inc., San Diego, CA), Sybyl (Tripos Associates) and Aladdin (Daylight Chemical
10   Information Systems, Irvine, CA).

Those skilled in the art will recognize that the design of a mimetic may require slight structural alteration or adjustment of a chemical structure designed or identified using the methods of the invention.

The invention may be implemented in hardware or software, or a
15   combination of both. However, preferably, the invention is implemented in computer programs executing on programmable computers each comprising a processor, a data storage system (including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. Program code is applied to input data to perform the
20   functions described above and generate output information. The output information is applied to one or more output devices, in known fashion. The computer may be, for example, a personal computer, microcomputer, or workstation of conventional design.

Each program is preferably implemented in a high level procedural or
25   object-oriented programming language to communicate with a computer system. However, the programs can be implemented in assembly or machine language, if desired. In any case, the language may be compiled or interpreted language.

Each such computer program is preferably stored on a storage
30   medium or device (e.g., ROM or magnetic diskette) readable by a general or special purpose programmable computer, for configuring and operating the computer when the storage media or device is read by the computer to perform the procedures described herein. The inventive system may also be considered to be implemented as a computer-readable storage medium,
35   configured with a computer program, where the storage medium so

configured causes a computer to operate in a specific and predefined manner to perform the functions described herein.

Compounds designed according to the methods of the present invention may be assessed by a number of *in vitro* and *in vivo* assays of
5   hormone function. For example, the identification of IGF-1R antagonists of may be undertaken using a solid-phase receptor binding assay. Potential antagonists may be screened for their ability to inhibit the binding of europium-labelled IGF ligands to soluble, recombinant IGF-1R in a microplate-based format. Europium is a lanthanide fluorophore, the presence
10 of which can be measured using time-resolved fluorometry. The sensitivity of this assay matches that achieved by radioisotopes, measurement is rapid and is performed in a microplate format to allow high-sample throughput, and the approach is gaining wide acceptance as the method of choice in the development of screens for receptor agonists/antagonists (see Apell et.al. J.
15 Biomolec. Screening 3:19-27, 1998 : Inglese et. al. Biochemistry 37:2372-2377, 1998).

Binding affinity and inhibitor potency may be measured for candidate inhibitors using biosensor technology.

The IGF-1R antagonists may be tested for their ability to modulate
20 receptor activity using a cell-based assay incorporating a stably transfected, IGF-1-responsive reporter gene [Souriau, C., Fort, P., Roux, P., Hartley, O., LeFranc, M-P. and Weill, M., 1997, Nucleic Acids Res. 25, 1585-1590]. An IGF-1-responsive, luciferase reporter gene has been assembled and transfected in 293 cells. The assay addresses the ability of IGF-1 to activate
25 the reporter gene in the presence of novel ligands. It offers a rapid (results within 6-8 hours of hormone exposure), high-throughput (assay can be conducted in a 96-well format for automated counting) analysis using an extremely sensitive detection system (chemiluminescence). Once candidate compounds have been identified, their ability to antagonise signal
30 transduction via the IGF-1R can be assessed using a number of routine *in vitro* cellular assays such as inhibition of IGF-1-mediated cell proliferation, induction of apoptosis in the presence of IGF-1 and the ablation of IGF-1-driven anchorage-independent cell growth in soft agar [D'Ambrosio, C., Ferber, A., Resnicoff, M. and Baserga, R., 1996, Cancer Res. 56, 4013-4020].
35 Such assays may be conducted on the P6 cell line, a cell line highly responsive to IGF as a result of the constitutive overexpression of the IGF-1R

(45-50,000 receptors/cell, [Pietrzkowski, Z., Sell, C., Lammers, R., Ullrich, A. and Baserga, R.,1992, Cell Growth.Diff. 3, 199-205]). Ultimately, the efficacy of any antagonist as a tumour therapeutic may be tested *in vivo* in animals bearing tumour isografts and xenografts as described [Resnicoff. M.. Burgaud,

5   J-L., Rotman, H. L., Abraham, D. and Baserga, R., 1995, Cancer Res. 55, 3739-3741; Resnicoff, M., Sell, C., Rubini, M., Coppola, D., Ambrose, D., Baserga, R. and Rubin, R., 1994 Cancer Res. 54: 2218-2222].

      Tumour growth inhibition assays may be designed around a nude mouse xenograft model using a range of cell lines. The effects of the receptor

10   antagonists and inhibitors may be tested on the growth of subcutaneous tumours.

      A further use of the structure of the IGF-1R fragment described here is in facilitating structure determination of a related protein, such as a larger fragment of this receptor, another member of the insulin receptor family or a

15   member of the EGF receptor family. This new structure may be either of the protein alone, or in complex with its ligand. For crystallographic analysis this is achieved using the method of molecular replacement (Brunger, Meth. Enzym. 1997 276 558-580, Navaza and Saludjian, *ibid.* 581-594, Tong and Rossmann, *ibid.* 594-611, Bentley, *ibid.* 611-619) in a program such as

20   XPLOR. In this procedure diffraction data is collected from a crystalline protein of unknown structure. A transform of these data (Patterson function) is compared with a Patterson function calculated from a known structure. Firstly, the one Patterson function is rotated on the other to determine the correct orientation of the unknown molecule in the crystal. The translation

25   function is then calculated to determine the location of the molecule with respect to the crystal axes. Once the molecule has been correctly positioned in the unit cell initial phases for the experimental data may be calculated. These phases are necessary for calculation of an electron density map from which structural differences may be observed and for refinement of the

30   structure. Due to limitations in the method the search molecule must be structurally related to that which is to be determined. However it is sufficient for only part of the unknown structure (e.g. < 50%) to be similar to the search molecule. Thus the three dimensional structure of IGF-1R residues 1-462 may be used to solve structures consisting of related receptors,

35   enabling a program of drug design as outlined above.

In summary, the general principles of receptor-based drug design can be applied by persons skilled in the art, using the crystallographic results presented above, to produce ligands of IGF-1R or other related receptors, having sufficient stereochemical complementarity to exhibit high affinity
5   binding to the receptor site.

The present invention is further described below with reference to the following, non-limiting examples.

EXAMPLE 1

10 <u>Expression, Purification and Crystallization of the IGF-1R Fragment.</u>

Several factors hamper macromolecular crystallization including sample selection, purity, stability, solubility (McPherson, A., et al., 1995, Structure 3:759-768); Gilliland, G. L., & Ladner, J. E., 1996, Curr. Opin. Struct. Biol. 6:595-603), and the nature and extent of glycosylation (Davis, S.
15 J., et al., 1993, Protein Eng. 6:229-232). Initial attempts to obtain structural data from soluble IGF-1R ectodomain (residues 1-906) protein, expressed in Lec8 cells (Stanley, P. 1989, Molec. Cellul. Biol. 9:377-383) and purified by affinity chromatography, produced large, well-formed crystals (1.0 mm x 0.2 mm x 0.2 mm) which gave no discernible X-ray diffraction pattern
20 (unpublished data). Similar difficulties have been encountered with crystals of the structurally-related epidermal growth factor receptor (EGFR) ectodomain, which diffracted to only 6 Å, insufficient for the determination of an atomic resolution structure (Weber, W. et al., 1994, J Chromat 679:181-189). This prompted us to search for a fragment of IGF-1R that was more
25 amenable to X-ray crystallographic studies.

The fragment expressed (residues 1-462) comprises the L1-cysteine-rich-L2 region of the ectodomain. The selected truncation position at Val462 is four residues downstream of the exon 6/exon 7 junction (Abbott, A. M., et al., 1992, J Biol Chem. 267:10759-10763), and occurs at a position where the
30 sequences of the IR and the structurally related EGFR families diverge markedly (Lax, I., et al., 1988, Molec Cell Biol. 8:1970-1978; Ward, C. W., et al., 1995, Proteins: Struct., Funct., Genet. 22:141-153), suggesting that it represents a domain boundary. The expression strategy included use of the pEE14 vector (Bebbington, C. R. & Hentschel, C. C. G., 1987, In: Glover, D.
35 M., ed. DNA Cloning. Academic Press, San Diego. Vol 3, p163) in glycosidase-defective Lec8 cells (Stanley, P., 1989, Molec. Cellul. Biol. 9:377-

383), which produce N-linked oligosaccharides lacking the terminal galactose and N-acetylneuraminic acid residues (Davis, S. J., et al., 1993, Protein Eng. 6:229-232; Liu, T., et al., 1996, J Biol Chem 271:33639-33646.). The construct contained a C-terminal c-myc affinity tag (Hoogenboom, H. R., et al., 1991,

5 Nucl Acids Res. 19:4133-4137), which facilitated immunoaffinity purification by specific peptide elution and avoided aggressive purification conditions. These procedures yielded protein which readily crystallized after a further gel filtration purification step. This provided a general protocol to enhance crystallisation prospects for labile, multidomain glycoproteins.

10 The structure of this fragment is of considerable interest, since it contains the major determinants governing insulin and IGF-1 binding specificity (Gustafson, T. A. & Rutter, W. J., 1990, J. Biol. Chem. 265:18663-18667; Andersen, A. S., et al., 1990, Biochemistry, 29:7363-7366; Schumacher, R., et al., 1991, J. Biol. Chem. 266:19288-19295; Schumacher,

15 R., et al., 1993, J. Biol. Chem. 268:1087-1094; Schäffer, L., et al., 1993, J. Biol. Chem. 268:3044-3047; Williams, P. F., et al., 1995, , J. Biol. Chem. 270:3012-3016), and is very similar to an IGF-1R fragment (residues 1-486) reported to act as a strong dominant negative for several growth functions and which induces apoptosis of tumour cells *in vivo* (D'Ambrosio, C., et al., 1996,

20 Cancer Res. 56:4013-4020).
The expression plasmid pEE14/IGF-1R/462 was constructed by inserting the oligonucleotide cassette:

AatII

25 5' GACGTC GACGATGACGATAAG GAACAAAAACTCATC
         D   V   D   D   D   D   K   E   Q   K   L   I
              (EK cleavage)   (c-myc tail)
        S   E   E   D   L   N   (Stop)
    TCAGAAGAGGATCTGAAT TAGAATTC GACGTC 3'
30   *EcoRI*   *AatII*

encoding an enterokinase cleavage site, c-myc epitope tag (Hoogenboom, H. R., et al., 1991, Nucleic acids Res. 19:4133-4137) and stop codon into the AatII site (within codon 462) of Igf-1r cDNA in the mammalian expression

35 vector pECE (Ebina, Y., et al., 1985, Cell, 40:747-758; kindly supplied by W. J. Rutter, UCSF, USA), and introducing the DNA comprising the 5' 1521 bp of

the cDNA (Ullrich, A., et al., 1986, EMBO J. 5:2503-2512) ligated to the
oligonucleotide cassette into the EcoRI site of the mammalian plasmid
expression vector pEE14 (Bebbington, C. R. & Hentschel, C. C. G., 1987, In:
Glover. D. M., ed. DNA Cloning. Academic Press, San Diego. Vol 3, p163;

5   Celltech Ltd., UK). Plasmid pEE14/IGF-1R/462 was transfected into Lec8
mutant CHO cells (Stanley, P. 1989, Molec. Cellul. Biol. 9:377-383) obtained
from the American Tissue Culture Collection (CRL:1737), using Lipofectin
(Gibco-BRL). Cell lines were maintained after transfection in glutamine-free
medium (Glascow modification of Eagle's medium (GMEM; ICN Biomedicals,

10   Australia) and 10% dialysed FCS (Sigma, Australia) containing 25 µM
methionine sulphoximine (MSX; Sigma, Australia) as described (Bebbington,
C. R. & Hentschel, C. C. G., 1987, In: Glover, D. M., ed. DNA Cloning.
Academic Press, San Diego. Vol 3, p163). Transfectants were screened for
protein expression by Western blotting and sandwich enzyme-linked

15   immunosorbent assay (ELISA) (Cosgrove, L., et al., 1995,) using monoclonal
antibody (Mab) 9E10 (Evan et al., 1985) as the capture antibody, and either
biotinylated anti-IGF-1R Mab 24-60 or 24-31 for detection(Soos et al., 1992;
gifts from Ken Siddle, University of Cambridge, UK). Large-scale cultivation
of selected clones expressing IGF-1R/462 was carried out in a Celligen Plus

20   bioreactor (New Brunswick Scientific, USA) containing 70 g Fibra-Cel Disks
(Sterilin, UK) as carriers in a 1.25 L working volume. Continuous perfusion
culture using GMEM medium supplemented with non-essential amino acids,
nucleosides, 25 µM MSX and 10% FCS was maintained for 1 to 2 weeks
followed by the more enriched DMEM/F12 without glutamine, with the same

25   supplemention for the next 4-5 weeks. The fermentation production run was
carried out three times under similar conditions, and resulted in an estimated
overall yield of 50 mg of receptor protein from 430 L of harvested medium.
Cell growth was poor during the initial stages of the fermentation when
GMEM medium was employed, but improved dramatically following the

30   switch to the more enriched medium. Target protein productivity was
essentially constant during the period from ~100 to 700 h of the 760 h
fermentation, as measured by ELISA using Mab 9E10 as the capture antibody
and biotinylated Mab 24-31 as the developing antibody.
        Soluble IGF-1R/462 protein was recovered from harvested

35   fermentation medium by affinity chromatography on columns prepared by
coupling Mab 9E10 to divinyl sulphone-activated agarose beads (Mini Leak;

22

Kem En Tec, Denmark) as recommended by the manufacturer. Mini-Leak Low and Medium affinity columns with antibody loadings of 1.5-4.5 mg/ml of hydrated matrix were obtained, with the loading range of 2.5-3 mg/ml giving optimal performance (data not shown). Mab 9E10 was produced by growing

5   hybridoma cells (American Tissue Culture Collection) in serum-free medium in the Celligen Plus bioreactor and recovering the secreted antibody (4 g) using protein A glass beads (Prosep-A, Bioprocessing Limited, USA). Harvested culture medium containing IGF-1R/462 protein was adjusted to pH 8.0 with Tris-HCl (Sigma), made 0.02% (w/v) in sodium azide and passed at

10   3-5 ml/min over 50 ml Mab 9E10 antibody columns at 4° C. Bound protein was recovered by recycling a solution of 2-10 mg of the undecamer c-myc peptide EQKLISEEDLN (Hoogenboom et al., 1991) in 20 ml of Tris-buffered saline containing 0.02% sodium azide (TBSA). Between 65% and 75% of the product was recovered from the medium as estimated by ELISA, with a

15   further 15-25% being recovered by a second pass over the columns. Peptide recirculation ($\sim$10 times) through the column eluted bound protein more efficiently than a single, slower elution. Residual bound protein was eluted with sodium citrate buffer at pH 3.0 into 1 M Tris HCl pH 8.0 to neutralize the eluant, and columns were re-equilibrated with TBSA.

20   Gel filtration over Superdex S200 (Pharmacia, Sweden), of affinity-purified material showed a dominant protein peak at $\sim$63 kDa, together with a smaller quantity of aggregated protein (Figure 3a). The peak protein migrated primarily as two closely spaced bands on reduced , sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE; Figure 3b), reacted

25   positively in the ELISA with both Mab 24-60 and Mab 24-31, and gave a single sequence corresponding to the N-terminal 14 residues of IGF-1R. No binding of IGF-1 or IGF-2 could be detected in the solid plate binding assay (Cosgrove et al., 1995, Protein Express Purif. 6:789-798). The IGF-1R/462 fragment was further purified by ion-exchange chromatography on Resource

30   Q (Pharmacia, Sweden). Using shallow salt gradients, protein enriched in the slowest migrating SDS-PAGE band was obtained (data not shown), which formed relatively large, well-formed crystals (see below). Isoelectric focussing showed the presence of one major and two minor isoforms. Protein purified on Resource Q with an isocratic elution step of 0.14 M NaCl in 20

35   mM TrisCl at pH 8.0 (fraction 2, Figure 4) showed less heterogeneity on isoelectric focussing (Figure 4 inset) and SDS-PAGE (data not shown), and

produced crystals of sufficient quality for structure determination (see below).

Crystals were grown by the hanging drop vapour diffusion method using purified protein concentrated in Centricon 10 concentrators (Amicon Inc, USA) to 5-10 mg/ml in 10-20 mM Tris-HCl pH 8.0 and 0.02% (w/v) sodium azide, or 100 mM ammonium sulfate and 0.02% (w/v) sodium azide. Crystallization conditions were initially identified using the factorial screen (Jancarik, J. & Kim, S.-H.,1991, J Appl Cryst 24:409-411).and then optimised. Crystals were examined on an M18XHF rotating anode generator (Siemens, Germany) equipped with Franks mirrors (MSC, USA) and RAXIS IIC and IV image plate detectors (Rigaku, Japan).

From the initial crystallization screen of this protein, crystals of about 0.1 mm in size grew in one week. Upon refining conditions, crystals of up to 0.6 x 0.4 x 0.4 mm could be grown from a solution of 1.7-2.0 M ammonium sulfate, 0.1 M HEPES pH 7.5. The crystals varied considerably in shape and diffraction quality, growing predominantly as rhombic prisms with a length to width ratio of up to 5:1, but sometimes as rhombic bipyramids, the latter form being favoured when using material which had been eluted from the Mab 9E10 column at pH 3.0. Each crystal showed a minor imperfection in the form of very faint lines from the centre to the vertices. Protein from dissolved crystals did not appear to be different from the protein stock solution when run on an isoelectric focusing gel. Upon X-ray examination, the crystals diffracted to 3.0-4.0 Å and were found to belong to the space group $P2_12_12_1$ with a = 76.8 Å, b = 99.0 Å, c = 119.6 Å. In the diffraction pattern, the crystal variability noted above was manifest as a large (1-2°) and anisotropic mosaic spread, with concomitant variation in resolution. To improve the quality of the crystals, they were grown in the presence of various additives or were recrystallized. These methods failed to substantially improve the crystal quality although bigger crystals were obtained by recrystallization. The variability in crystal quality appeared to be due to protein heterogeneity, as demonstrated by the observation that more highly purified protein, eluted isocratically from the Resource Q column and showing one major band on isoelectric focusing (Figure 4 inset), produced crystals of sufficient quality for structure determination. These crystals diffracted to 2.6 Å resolution with cell dimensions, a = 77.0 Å, b = 99.5 Å, c = 120.1 Å and mosaic spread of 0.5°. Heavy metal derivatives of the IGF-

1R/462 crystals have been obtained and are leading to the determination of an atomic resolution structure of this fragment, which contains the L1, cysteine-rich and L2 domains of human IGF-1R.

5

EXAMPLE 2
Structure of the IGF-1R/1-462

Crystals were cryo-cooled to -170°C in a mother liquor containing 20% glycerol, 2.2 M ammonium sulfate and 100 mM Tris at pH 8.0. Native and
10   derivative diffraction data were recorded on Rigaku RAXIS IIc or IV area detectors using copper Kα radiation from a Siemens rotating anode generator with Yale/MSC mirroroptics. The space group was $P2_12_12_1$ with a = 77.39 Å, b = 99.72 Å, and c = 120.29 Å. Data were reduced using DENZO and SCALEPACK (Otwinowski, Z. & Minor, W., 1996, Mode.Meth. Enzym.
15   276:307-326). Diffraction was notably anisotropic for all crystals examined.

Phasing by multiple isomorphous replacement(MIR) was performed with PROTEIN (Steigeman, W. Dissertation (Technical Univ. Munich, 1974) using anomalous scattering for both UO2 and PIP derivatives. Statistics for data collection and phasing are given in Table 1. In the initial MIR map
20   regions of protein and solvent could clearly be seen, but the path of the polypeptide was by no means obvious. That map was subject to solvent flattening and histogram matching in DM (Cowtan, K.,1994, Joint CCP4 and ESF-EACBM newslett. Protein Crystallogr. 31:34-38). The structure was traced and rebuilt using O (Jones, T. A., et al., 1991, Acta Crystallogr.
25   A47:110-119) and refined with X-PLOR 3.851 (Brunger, A. T., 1996, X-PLOR ReferenceManual 3.851, Yale Univ., New Haven, CT). After 5 rounds of rebuilding and energy minimisation the R-factor dropped to 0.279 and Rfree = 0.359 for data 7-2.6 Å resolution. The current model contains 458 amino acids and 3 N-linked carbohydrates but no solvent molecules. For residues
30   with B(Ca) > 70, Å atomic positions are less reliable (37-42, 155-159, 305, 336-341, 404-406,453-458). There is weak electron density for residues 459-461, but the c-myc tail appears completely disordered.

The 1-462 fragment consists of the N-terminal three domains of IGF-1R (L1, cys-rich, L2), and contains regions of the molecule which dictate
35   ligand specificity (17-23). The molecule adopts a reasonably extended structure (approximately 40 x 48 x 105 Å) with domain 2 (cys-rich region)

making contact along the length of domain 1 (L1) but very little contact with the third domain (L2) (see Figure 5). This leaves a space at the centre of the molecule of approximately 24 Å x 24 Å x 24 Å which is bounded on three sides by the three domains of the molecule. The space is of sufficient size to accommodate the ligand, IGF-1.

Table 1 Summary of Crystallographic data

Data set[a]	Resol. (Å)	Mean I/s	R_{merge}[b]	Completeness (multiplicity)	No. of sites	R_{cullis}[c]	Phasing power[d]	FOM[e]
Native	2.6	18.7	0.064	0.996 (4.1)				0.47 / 0.71
PIP	3.0	15.8	0.060	0.982 (2.2)	3	0.66	1.71	
UO2Ac2	4.5	7.5	0.095	0.989 (2.3)	2	0.82	1.17	

Refinement resolution (Å)	No of refl. (free)	No. of Atoms	R_{cryst}[f]	R_{free}[f]	Bonds[g] (Å)	Angles[g] (Å)
7.0-2.6	24270 (2693)	3903	0.237	0.304	0.017	0.048

a PIP, Di-μ-iodobis(ethylenediamine)diplatinum dinitrate; UO2Ac2, Uranyl acetate.

b $R_{merge} = \Sigma_h \Sigma_j |I_{h,j} - I_h| / \Sigma_h \Sigma_j I_h$. where $I_{h,j}$ is an intensity measurement j and I_h is the mean intensity for that reflection h.

c $R_{cullis} = \Sigma_h ||F_{PH} - F_P| - |F_{Hcalc}||/\Sigma_h||F_{PH}| - |F_P||$, where F_{PH}, F_P and F_{Hcalc} are, respectively, derivative, native and heavy atom structure factors for centric reflections h.

d Phasing power = $\Sigma_h |F_{Hcalc}|/\Sigma_h \varepsilon$. where F_{Hcalc} is defined above and ε is the lack of closure.

e FOM(figure of merit) = $<\cos(\Delta\alpha_h)>$. where $\Delta\alpha_h$ is the error in the phase angle for reflection h. Values are given before and after density modification at 3.0 and 2.8 Å resolution, respectively.

f R_{cryst} and R_{free} are defined in Brunger, A.T. *XPLOR* reference manual 3.851 (Yale Univ., New Haven, CT, 1996)

8 r.m.s. deviation from ideal bond and angle-related (1-3) distances.

The L domains

Each of the L domains (residues 1-150 and 300-460) adopts a compact
shape (24 x 32 x 37 Å) consisting of a single-stranded right handed β-helix
and capped on the ends by short α-helices and disulfide bonds. The body of
the domain looks like a loaf of bread, with the base formed from a flat six-
stranded β-sheet, 5 residues long and the sides being β-sheets three residues
long (Figures 5 & 6). The top is irregular, but in places is similar for the two
domains. The two domains are superposable with an rms deviation in Cα
positions of 1.6 Å for 109 atoms (Figure 7). Although this fold is reminiscent
of other β-helix proteins it is much simpler and smaller with very few
elaborations, and thus it represents a new superfamily of domains. One
notable difference between the two domains is that the indole ring of Trp 176
from the cys-rich region (Figure 6b) is inserted into the hydrophobic core of
L1, and the C-terminal helix is only vestigial (Figure 8). For the insulin
receptor family the sequence motif of residues which form the Trp pocket in
L1 does not occur in L2 (Figure 6a). However in the EGF receptor, which has
an additional cys-rich region after the L2 domain (14, 15), the pocket motif
can be found in both L domains and the Trp is conserved in both cys-rich
regions (Figure 6b).

The repetitive nature of the β-helix is reflected in the sequence and
the first five turns were correctly identified by Bajaj, M., et al. (1987,
Biochim.Biophys. Acta 916:220-226), the conserved Gly residues being found
in turns making one bottom edge of the domain. However, their conclusions
about the fold were incorrect. The"helix-like" repeat is actually a pair of
bends at the top edge of the domain. In their Motif V, the Gly is not in a
bend but is followed by the insertion of a conserved loop of 7-8 residues (see
Figure 6a). Glycine is structurally important in the Gly bends as mutation of
these residues compromises folding of the receptor [van der Vorm, E.R., et
al., 1992, J. Biol. Chem. 267, 66-71; Wertheimer, E. et al., 1994, J. Biol. Chem.
269, 7587-7592].

Comparison of the L domains with other right-handed β-helix
structures such as pectate lyase (Yoder, M. D., et al., 1993,.Structure, 1:241-
251-1507) and the p22 tailspike protein (Steinbacher, S., et al., 1997, J.Mol.
Biol. 267:865-880) shows some striking similarities as well as differences. In

all cases the ends of the domain are capped by α-helices, but the L domains also have a disulphide bond at each end to hold the termini. The other β-helix domains are considerably longer and have significant twist to their sheets, while the L domains have flat sheets. Although the sizes of the helix

5   repeats are similar (here 24-25 residues vs 22-23 for pectate lyase) the cross-sections are quite different. The L domains have a rectangular cross-section, while pectate lyase and p22 tailspike protein are V-shaped, and have many, and sometimes quite large, insertions (Yoder, M. D., et al., 1993, Structure, 1:241-251-1507; Steinbacher, S., et al., 1997, J.Mol. Biol. 267:865-880). In

10   the hydrophobic core a common feature is the stacking of aliphatic residues from successive turns of the β-helix, and near the C-terminus of each L domain there is also a short Asn ladder, reminiscent of the long Asn ladder observed in pectate lyase (Yoder, M. D., et al., 1993, Structure 1:241-251-1507). On the opposite side of the L domains the Gly bend, as well as the

15   two bends and sheet preceding it, have no counterpart in the other β-helix domains. Thus although the L domains are built on similar principles to the other β-helix domains they constitute a separate superfamily.

The cys-rich domain

The cys-rich domain is composed of eight disulfide-bonded modules (Figure

20   6b), the first of which sits at the end of L1, while the remainder make a curved rod running diagonally across L1 and reaching to L2 (Figure 5). The strands in modules 2-7 run roughly perpendicular to the axis of the rod in a manner more akin to laminin (Stetefeld, J., et al.,1996, J.Mol.Biol. 257:644-657) than to TNF receptor (Banner, D. W., et al., 1993, Cell, 73:431-445), but

25   the modular arrangement of the cys-rich domain is different to those of other cys-rich proteins for which structures are known. The first 3 modules of IGF-1R have a common core, containing a pair of disulfide bonds, but show considerable variation in the loops (Figure 6b). The connectivity of these modules is the same as in the first half of EGF (Cys 1-3and 2-4). but their

30   structures do not appear to be closely related to any member of the EGF family. Modules 4 to 7 have a different motif, a β-finger, and best match residues 2152-2168 of fibrillin (Dowling, A. K., et al., 1996. Cell, 85:597-605). Each is composed of three polypeptide strands, the first and third being disulfide bonded and the latter two forming a β-ribbon. The β-ribbon of each

35   β- finger module lines up antiparallel to form a tightly twisted 8-stranded β-sheet (Figures 5 and 8). Module 6 deviates from the common pattern,with

the first segment being replaced by an α-helix followed by a large loop that is likely to have a role in ligand binding (see below). As module 5 is most similar to module 7 it is possible that the four modules arose from serial gene duplications. The final module is a disulfide-linked bend of five residues.

5   The fact that the two major types of cys-rich modules occur separately implies that these are the minimal building blocks of cys-rich domains found in many proteins. Although it can be as short as 16 residues, the motif of modules 4-7 is clearly distinct, and capable of forming a regular extended structure. Thus cys-rich domains such as these can be considered
10   as being made of repeat units each composed of a small number of modules.

Hormone binding

          Attempts have been made to locate the IGF-1 (and insulin) binding site by examining natural (Taylor, S. I., 1992, Diabetes, 41:1473-1490) and site-directed mutants (Williams, P. F., et al., 1995, J. Biol. Chem. 270:3012-
15   3016; Mynarcik, D. C et al., 1996, J. Biol. Chem. 271:2439-2442; Mynarcik, D. C., et al., 1997, J. Biol. Chem. 272:2077-2081), chimeric receptors (Andersen, A. S., et al., 1990, Biochemistry 29:7363-7366; Gustafson, T. A., & Rutter, W. J., 1990, J. Biol. Chem. 265:18663-18667; Schäffer, L., et al.,1993, J. Biol. Chem. 268:3044-3047; Schumacher, R., 1993, J. Biol. Chem. 268:1087-1094;
20   Kjeldsen, T., et al., 1991, Proc. Natl Acad. Sci. USA, 88:4404-4408) and by crosslinking studies (Wedekind, F., et al., 1989, Biol. Chem Hoppe-Seyler, 370:251-258; Fabry, M., 1992, J. Biol. Chem. 267:8950-8956; Waugh, S. M., et al., 1989, Biochemistry, 28:3448-3458; Kurose, T., et al., 1994),.J. Biol. Chem.269:29190-29197-34). IGF-1R/IR chimeras not only show which
25   regions of the receptors account for ligand specificity, but also provide an efficient means of identifying some parts of the hormone binding site. Paradoxically, regions controlling specificity are not the same for insulin and IGF-1. Replacing the first 68 residues of IGF-1R with those of IR confers insulin-binding ability on the chimeric IGF-1R (Kjeldsen, T., et al., 1991,
30   Proc. Natl Acad. Sci. USA, 88:4404-4408), and replacing residues 198-300 in the cys-rich region of IR with the corresponding residues 191-290 of IGF-1R allows the chimeric receptor to bind IGF-1 (Schäffer, L., et al.,1993, J. Biol. Chem. 268:3044-3047). Thus a receptor can be constructed which binds both IGF-1 and insulin with near native affinity. From the structure it is clear that
35   if the hormone bound in the central space it could contact both these regions.

From analysis of a *series of chimeras* examined by Gustafson, T. A., & Rutter, W. J. (J. Biol. Chem. 265:18663-18667, 1990), the specificity determinant in the cys-rich region can be limited further to residues 223-274. This region corresponds to modules 4-6, and includes a large and somewhat

5   mobile loop (residues 255-263, mean B[Cα atoms] = 57 Å2) which extends into the central space (see Figure 5). In IR this loop is four residues bigger, and is stabilised by an additional disulfide bond (Schäffer, L. & Hansen, P.H.,1996, Exp. Clin. Endocrinol. Diabetes, 104: Suppl. 2, 89). The larger loop of IR may serve to exclude IGF-1 from the hormone binding site while

10   allowing the smaller insulin molecule to bind. It is interesting to note that mosquito IR homologue, which has a loop two residues larger than the mammalian IRs, also appears to bind insulin but not IGF-1 (Graf, R., et al., 1997, Insect Molec.Biol. 6:151-163). Analysis of the structure indicates that the insulin/IGF-1 specificity is controlled by residues in this loop (amino

15   acids 253-272 in IGF-1R; amino acids 260-283 in IR)

As chimeras only address residues which differ between the two receptors, a more precise analysis of the site can be obtained from single site mutants. In particular, from an alanine-replacement study, four regions of L1 important for insulin binding were identified (Williams, P. F., et al., 1995, J.

20   Biol. Chem. 270:3012-3016). The first three are at similar positions on successive turns of the β-helix and the fourth lies on the conserved bulge on the large β-sheet. Thus there is a footprint for insulin binding to the L1 domain which lies on the first half of the large β-sheet facing into the central space. Residues further along the sheet which are conserved in IGF-1R could

25   also be important. The conservative substitution of leucine for methionine at residue 119 of IR (113 of IGF-1R) causes a mild form of leprechaunism [Hone, J. et al., 1994, J. Med. Genet. 31, 715-716]. This residue is buried, and the mutation could perturb neighbouring residues to affect insulin binding.

The axis of the L2 domain is perpendicular to that of the L1 domain,

30   and the N-terminal end of its β-helix is presented to the hormone-binding site. On this face of the L2 domain the only mutation studied so far is the naturally occurring IR mutant, S323L, which gives rise to Rabson-Mendehall syndrome and severe insulin resistance (Roach, P.,1994, Diabetes 43:1096-1102). As this mutant only affects insulin binding and not cell-surface

35   expression, residue 323 of IR (residue 313 of IGF-1R) is probably at or near the binding site. Structurally this residue lies in the middle of a region

(residues 309-318 of IGF-1R) which is conserved in both IR and IGF-1R, and
the surrounding region, 332-345 (of IGF-1R), is also quite well conserved in
the these receptors (Figure 6a). Therefore this region is quite likely to form
part of the hormone-binding site, but would not have been detected by

5   chimeras. It is interesting to note that in this region IRR is not as well
conserved as the other two receptors (Shier, P. & Watt, V.M., 1989,
J.Biol.Chem. 264:4605-14608).

The distance from this putative hormone-binding region on L2 to that
found on L1 is about 30 Å (Figure 5). Thus L1 and L2 appear too far apart to

10   bind IGF-1 or insulin. However, in the crystal structure there is a deep cleft
between part of the cys-rich domain (residue 262)and L2 (residue 305), and
this cleft is occupied by a loop from a neighbouring molecule. Thus it seems
probable that the position of the L2 domain in the receptor structure or the
hormone-receptor complex adopts a different position with respect to the

15   cys-rich domain than that found in the crystal. The movement required to
bring L2 sufficiently close to L1 is small, namely a rotation of approximately
25° about residue 298.

A number of IR mutants have been identified which constitutively
activate the receptor, and the majority of these are found in the α chain.

20   Curiously all α chain mutants involve changes to or from proline or the
deletion of an amino acid, implying that they cause local structural
rearrangements. The mutation R86N is similar to wild type, but R86P
reduces cell-surface expression and insulin binding while constitutively
activating autophosphorylation [Grønskov, K. et al., 1993, Biochem. Biophys.

25   Res. Commun. 192, 905-911]. The proline mutation probably disturbs
residues preceding 87 which lie in the interface between the L1 and cys-rich
domains, but it could also affect insulin binding. In the cys-rich domain
residues 233, 281, 244 and 247 of IR are not conserved in IGF-1R (Figure 6b),
yet L233P [Klinkhamer, M.P. et al., 1989, EMBO J. 8, 2503-2507], deletion of

30   N281 [Debois-Mouthon, C. et al., 1996, J. Clin. Endochronol. Metab. 81, 719-
727] or the triple mutant P243R, P244R and H247D [Rafaeloff, R. et al., 1989,
J. Biol. Chem. 264, 15900-15904] cause constitutive kinase activation. Due to
their locations each of these three mutants appears likely to compromise the
folding of a β-finger domain and, in turn, the structural integrity of the rod-

35   like cys-rich domain. The structural ramifications of these mutations could
be significant for the whole receptor ectodomain, as disturbing the L1/cys-

rich interface or distorting the rod-like domain could affect the relative position of L1 and the cys-rich domain in this context.

L1 has been further implicated, as deletion of K121 on the opposite side of L1 from the cys-rich domain was also found to cause autophosphorylation [Jospe, N. et al., 1994, J. Clin. Endochronol. Metab. 79, 1294-1302]. By contrast this mutation does not affect insulin binding. Thus a possible mechanism emerges for insulin binding and signal transduction. When insulin binds between L1 and L2 it modifies the relative position of L1 and the cys-rich domain in the receptor, perhaps by hinge motion between L2 and the cys-rich domain like that suggested above, and the structural rearrangement is transmitted across the plasma membrane. In the absence of insulin the same signal can be initiated by mutations in the cys-rich region or at the L1/cys-rich interface, but at the expense on insulin binding. The signal can also be initiated more directly by mutations on the opposite side of L1 which affect the interaction of L1 with other parts of the ectodomain, possibly the other half of the receptor dimer.

Ligand Studies

Although there is no structural information about an IGF-1/IGF-1R complex a number of studies have probed the nature of this interaction. Results from cross-linking experiments with IGF-1 and insulin and their cognate receptors are consistent with the hormone binding site proposed above. For example B29 of insulin can be cross-linked to the cys-rich region (residues 205-316((Yip, C. C., et al., 1988, Biochim. Biophys. Res. Commun. 157:321-329) or the L1 domain (Wedekind, F., et al., 1989, Biol. Chem Hoppe-Seyler, 370:251-258). However, these two regions are reasonably well separated, and those studies may indicate that B29 is mobile. Other studies unfortunately do not map the site any more precisely.

Analogues and site-directed mutants of IGF-1 and IGF-2 have been more fruitful. IGF-1 and IGF-2 contain two extra regions relative to insulin, the C region between B and A and a D peptide at the C-terminus. For IGF-1, replacement of the C region by a four Gly linker reduced affinity for IGF-1R by a factor of 40 but increased affinity for IR 5-fold (Bayne, M.L.,et al., 1988, J. Biol.Chem. 264:11004-11008). Changes in affinity are consistent with the deletion in IGF-1 complementing differences in the cys-rich regions of IGF-1R and IR noted above. Mutation of residues either side of the C region (residue 24 for IGF-1 [Cascieri, M.A., et al., 1988, Biochemistry 27:3229-

3233], residues 27,43 for IGF-2, [Sakano, K., et al., 1991, J. Biol. Chem. 266:20626-20635]) also has deleterious effects on the affinity of the hormone for IGF-1R, as has truncation of the nearby D peptide in IGF-2 (Roth, B.V., et al., 1991, Biochem. Biophys. Res. Commun. 181:907-914).

5   Insulin has been extensively mutated. Binding studies [summarised in Kristensen, C. et al., 1997, J. Biol. Chem. 272, 12978-12983] indicate that insulin may bind its receptor via a hydrophobic patch (residues A2, A3, A19, B8, B11, B12, B15 and possibly B23 & B24). However this patch is normally buried, and requires the removal of the B chain's C-terminus from the

10   observed position. Assuming IGF-1, IGF-2 and insulin bind their receptors in the same orientation, these data suggest an approximate orientation for the hormone when bound to the receptor.

One notable feature of IGF-1 and IGF-2 is the large number of charged residues and their uneven distribution over the surface. Basic

15   residues are predominantly found in the C region and, in solution, this region is not well ordered in either IGF-1 or -2 (Sato, A., et al., 1993, Int J Peptide Protein Res. 41:433-440; Torres, A. M., et al., 1995,J. Mol. Biol. 248:385-401). In contrast the binding site of the receptor has a sizable patch of acidic residues in the corner where the cys-rich domain departs from L1. Other

20   acidic residues which are specific to this receptor are found along the inside face of the cys-rich domain and the loop (residues 255-263) extending from module 6. Thus it is possible that electrostatic interactions play an important part in IGF-1 binding, with the C region binding to the acidic patch of the cys-rich region near L1 and the acidic patch on the other side of the

25   hormone directed towards a small patch of basic residues (residues 307-310) on the N-terminal end of L2.

Although the structure of this fragment gives significant information about the nature of the hormone binding site, residues outside this region have also been shown to affect binding of ligand. A number of studies have

30   implicated residues 704-715 of IR (Mynarcik, D. C et al., 1996, J. Biol. Chem. 271, 2439-2442; Kurose, T., et al., 1994, J. Biol. Chem.269:29190-29197). These residues could contact insulin on one of the sides left open in the current structure. Using insulin labelled at the B1 residue, Fabry, M., et al.,(1992, J. Biol. Chem. 267:8950-8956) cross-linked insulin to the fragment

35   390-488, part of which is not near the site as described. The explanation for this could be either the region 390-488 reaches back to the hormone binding

site, or this region could contact another hormone bound to the other half of the receptor. Further structural information is needed to establish how these other regions contact the hormone and to elucidate how binding of the hormone is communicated to the kinase inside the cell.

5   The structure of the L1-cys-rich-L2 domains of IGF-1R presented here represents the first structural information for the extracellular portion of a member of the insulin receptor family. The L domains display a novel fold which is common to the EGF receptor family, and the modular architecture of the cys-rich domain implies that smaller building blocks should be used to

10   describe the composition of cysteine-rich domains. This fragment contains the major specificity determinants of receptors of this class for their ligands. It has an elongated structure with a space in the middle which could accommodate the ligand. The three sides of this site correspond to regions which have been implicated in hormone binding. Although other sites are

15   present in the receptor ectodomain which interact with the ligand, this structure gives us an initial view of how the insulin, IGF-1 and IGF-2 might interact with their cell surface receptors to control their metabolic and mitogenic effects

           Such information will provide valuable insight into the structure of

20   the corresponding domains of the IR and insulin receptor-related receptor as well as members of the related EGFR family (Bajaj, M., et al., 1987, Biochim Biophys Acta 916:220-226; Ward, C. W. et al., 1995, Proteins: Struct Funct Genet 22:141-153).

EXAMPLE 3

25   **Prediction of 3D Structure of the Corresponding Domains of IRR and IR Based on Structure of IGF-1R Fragment.**

           The sequence identities between the different members of the insulin receptor family are sufficient to allow accurate sequence alignments to facilitate 3D structure predictions by homology modelling. The alignments of

30   the ectodomains of human IGF-1R, IR, and IRR are shown in Figure 9.

EXAMPLE 4

Single-Molecule Imaging of Human Insulin Receptor Ectodomain and its Fab Complexes

Cloning and expression of hIR -11 ectodomain protein

35   A full length clone of the human IR exon -11 form (hIR -11) was prepared by exchanging an Aat II fragment, nucleotides 1195 to 2987 , of the

exon +11 clone (plasmid pET; Ellis et al., 1986; gift from Dr W. J. Rutter, UCSF) of hIR (Ebina et al., 1985, *Cell* **40**, 747-758) with the equivalent Aat II fragment from a plasmid (pHIR/P12-1, ATCC 57493) encoding part of the extracellular domain and the entire cytoplasmic domain of hIR -11 (Ullrich

5   et al., 1985, *Nature* **313** , 756-761). The ectodomain fragment of hIR -11 (2901 bp, coding for the 27 residue signal sequence and residues His1-Asn914) was produced by SalI and SspI digestion and inserted into the mammalian expression vector pEE6.HCMV-GS (Celltech Limited, Slough, Berkshire, UK) into which a stop codon linker had been inserted, as

10   described previously (Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798) for the hIR exon +11 ectodomain.

The resulting recombinant plasmid pHIR II (2 µg) was transfected into glycosylation-deficient Chinese hamster ovary (Lec 8) cells (Stanley, 1989, *Molec. Cellul. Biol.* **9**, 377-383) with Lipofectin (Gibco-BRL). After

15   transfection, the cells were maintained in glutamine-free medium GMEM (ICN Biomedicals, Australia) as described previously (Bebbington & Hentschel, 1987, In *DNA Cloning* (Glover, D., ectodomain.), Vol III, Academic Press, san Diego; Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798). Expressing cell lines were selected for growth in GMEM with 25

20   µM methionine sulphoximine (MSX, Sigma). Transfectants were screened for protein expression using sandwich ELISA with anti-IR monoclonal antibodies 83-7 and 83-14. Metabolic labelling of cells, immunoprecipitations, insulin binding assays and Scatchard analyses were performed as described previously for the exon +11 form of hIR ectodomain (Cosgrove et al., 1995, ,

25   *Protein Expression and Purification* **6**, 789-798).

hIR -11 ectodomain production and purification

The selected clone (inoculum of 1.28 x 108 cells) was grown in a spinner flask packed with 10 g of Fibra-cel disc carriers (Sterilin, U.K.) in 500 ml of GMEM medium containing 10% fetal calf serum (FCS) and 25 µM MSX.

30   Selection pressure was maintained for the duration of the culture.

Ectodomain was recovered from harvested medium by affinity chromatography on immobilized insulin, and further purified by gel filtration chromatography on Superdex S200 (Pharmacia; 1 x 40 cm) in Tris-buffered saline containing 0.02% sodium azide (TBSA) as described previously

35   (Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798). Solutions of purified hIR -11 ectodomain were stored at 4° C prior to use.

Production of Fab fragments and their complexes with ectodomain

5   Purification of Mabs 83-7, 83-14 and 18-44 from ascites fluid by
affinity chromatography using Protein A-Sepharose, and the production of
Fabs, were based on the methodologies described in Coligan et al.,1993,
Current Protocols in Immunology, Vol 1, pp 2.7.1-2.8.9, Greene Publishing
10   Associates & Wiley - Interscience, John Wiley and Sons. Fab was produced
from monoclonal antibody by mercuripapain digestion for 1-4 h, followed by
gel filtration on Superdex S200. Products were monitored by reducing and
non-reducing SDS-PAGE. For 83-7 Mab, an IgG Type 1 monoclonal antibody,
the bivalent (Fab)2' isolated by this method was reduced to monovalent Fab
15   83-7 by mild reduction with mM L-cysteine.HCl in 100 mM Tris pH 8.0
(Coligan et al., 1993, Current Protocols in Immunology, Vol 1, pp 2.7.1-2.8.9,
Greene Publishing Associates & Wiley - Interscience, John Wiley and Sons).

          Complexes of Fab with hIR -11 ectodomain were produced by mixing
~ 2.5 to 3.5 molar excess of Fab with hIR -11 ectodomain at ambient
20   temperature in TBSA at pH 8.0. After 1-3 h, the complex was separated from
unbound Fab by gel filtration over a Superdex S200 column in the same
buffer.

Electron microscopy

          Uncomplexed hIR -11 ectodomain and the Fab complexes described
25   above were diluted in phosphate-buffered saline (PBS) to concentrations of
the order of 0.01-0.03 mg/ml. Prior to dilution, 10% glutaraldehyde (Fluka)
was added to the PBS to achieve a final concentration of 1% glutaraldehyde.
Droplets of ~ 3ml of this solution were applied to thin carbon film on 700-
mesh gold grids after glow-discharging in nitrogen for 30 s. After 1 min. the
30   excess protein solution was drawn off and followed by application and
withdrawal of 4-5 droplets of negative stain [2% uranyl acetate (Agar), 2%
uranyl formate (K and K), 2% potassium phosphotungstate (Probing and
Structure) adjusted to pH 6.0 with KOH, or 2% methylamine tungstate (Agar)
adjusted to pH 6.8 with NH4OH]. In the case of both uranyl acetate and
35   uranyl formate staining, an intermediate wash with 2 or 3 droplets of PBS
was included prior to application of the stain. The grids were air-dried and

then examined at 60kV accelerating voltage in a JEOL 100B transmission electron microscope at a magnification of 100,000x. It was found that there was a typical thickness of negative stain in which Fabs were most easily seen. Hence areas for photography had to be chosen from particular zones of
5   the grid. Electron micrographs were recorded on Kodak SO-163 film and developed in undiluted Kodak D19 developer. The electron-optical magnification was calibrated under identical imaging conditions by recording single-molecule images of the antigen-antibody complex of influenza virus neuraminidase heads and NC10 MFab (Tulloch et al., 1986, *J.Mol. Biol.* **190**,
10   215-225; Malby et al., 1994, *Structure*, **2**, 733-746).

Image processing

Electron micrographs showing particles in a limited number of identifiable projections were chosen for digitisation. Micrographs were digitised on a Perkin-Elmer model 1010 GMS PDS flatbed scanning
15   microdensitometer with a scanning aperture (square) size of 20 mm and stepping increment of 20 mm corresponding to a distance of 0.2 nm on the specimen. Particles were selected from the digitised micrograph using the interactive windowing facility of the SPIDER image processing system (Frank et al., 1996, *J. Struct. Biol.* **116**, 190-199). Particles were scaled to an optical
20   density range of 0.0 - 2.0 and aligned by the PSPC reference-free alignment algorithm (Marco et al., 1996, *Ultramicroscopy*, **66**, 5-10). Averages were then calculated over a subset of correctly aligned particles chosen interactively as being representative of a single view of the particle. The final average image presented here is derived from a library of 94 images.

25   **Biochemical characterization of expressed hIR -11 ectodomain**

The recombinant protein examined corresponded to the the first 914 residues of the 917 residue ectodomain of the exon -11 form of the human insulin receptor (Ullrich et al., 1986, *Nature* **313** , 756-761). Expressed protein was shown, by SDS-PAGE and autoradiography of immunoprecipitated
30   product from metabolically labelled cells, to exist as a homodimeric complex of ~270 - 320 kDa apparent mass, which dissociated under reducing conditions into monomeric α and β' subunits of respective apparent mass ~120 kDa and ~35 kDa (data not shown).

Purified hIR -11 ectodomain, expressed in Lec8 cells and purified by
35   affinity chromatography on an insulin affinity column, eluted as a symmetrical peak on a Superdex S200 gel filtration column (Figure 10). The

37

protein eluted with an apparent mass of ~400 kDa, calculated from a standard curve generated by the elution positions of standard proteins (not shown). As expected for protein expressed in Lec 8 cells, whose glycosylation defect produces truncated oligosaccharides (Stanley, 1989, .

5   *Molec. Cellul. Biol.* **9**, 377-383), this value is less than the apparent mass (450 - 500 kDa) reported for hIR +11 ectodomain expressed in wild-type CHO-K1 cells (Johnson et al., 1988, *Proc. Natl Acad. Sci USA* **85**, 7516-7520; Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798).

Radioassay of insulin binding to purified ectodomain gave linear

10   Scatchard plots and Kd values of 1.5 - 1.8 x 10-9 M, similar to the values of 2.4 - 5.0 x 10-9 M reported for the hIR -11 ectodomain (Andersen et al., 1990, *Biochemistry* **29**, 7363-7366; Markussen et al., 1991, *J. Biol. Chem.* **266**, 18814-18818; Schaffer, 1994, *Eur. J. Biochem.* **221**, 1127-1132) and the values of ~1.0 - 5.0 x 10-9 M reported for the hIR +11 ectodomain (Schaefer et al.,

15   1992, *J. Biol. Chem.* **267**, 23393-23402; Whittaker et al., 1994, *Molec. Endocrinol.* **8**, 1521-1527; Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798).

Expression of hIGF-1R ectodomain

Cloning, expression and purification of this protein used elements

20   common to those described for hIR -11 ectodomain (Cosgrove et al., 1995, *Protein Expression and Purification* **6**, 789-798), and resulted in purified product that was recognised by receptor-specific Mabs 17-69, 24-31 and 24-60 (Soos et al., 1992, *J. Biol. Chem.* **267**, 12955-63) and was composed of α and β' subunits of mass similar to those of hIR ectodomain.

25   Preparation of hIR -11 ectodomain/MFab complexes

A complex of hIR -11 ectodomain and Fab from antibody 83-14 eluted as a symmetrical peak of 460 -500 kDa (Figure 10), as did complexes generated from a mixture of hIR -11 ectodomain with Fab from antibody 18-44 and a mixture of hIR -11 ectodomain with Fab 83-7 (not shown). A co-

30   complex of ectodomain with Fabs from antibodies 18-44 and 83-14 eluted at ~ 620 kDa, as did a co-complex with MFabs 83-14/83-7 and another with MFabs 83-7/18-44 (not shown). A complex of hIR -11 ectodomain with all three MFab derivatives, 18-44, 83-7 and 83-14, eluted at an apparent mass of ~ 710 kDa (Figure 10).

35   **Electron microscopy**

Imaging of hIR -11 and hIGF-1R ectodomains

Single-molecule imaging of uncomplexed dimeric hIR -11
ectodomain was carried out under a variety of negative staining conditions,
which emphasised different aspects of the structure of the molecular
envelope. Images obtained by this investigation are depicted in Figure 11.

5   The least aggressive or penetrative stain was potassium
phosphotungstate (KPT) , which revealed consistent globular particles with
very little internal structure other than a suggestion of a division into two
parallel bars. Staining with methylamine tungstate also revealed the parallel
bar images.

10   Further investigation using progressively more penetrative, but also
potentially more disruptive, stains confirmed the observations above.
Staining with uranyl acetate and uranyl formate showed the separation of the
parallel bars most clearly, but uranyl acetate showed evidence of disrupting
the structure of the particles, i.e. a decrease in the consistency of the particle
15   shape and a tendency for particles to look unravelled or denatured despite
having been subjected to chemical cross-linking prior to staining. In areas of
thicker stain, parallel bars predominated, whereas in more thinly stained
regions, U-shaped particles could be identified, sometimes outnumbering the
parallel-bar structures (see Figure 11).

20 **Imaging of hIR -11 ectodomain complexed with 83-7 MFab**

This complex was particularly noteworthy for the consistency of the
form of the particles, especially under the gentler staining conditions
afforded by stains such as KPT and methylamine tungstate. The particles
were interpreted as having been restricted in the views they presented, after
25   air-drying on the carbon support film, by the almost diametrically opposite
binding of the two Fab arms to the antigen to form a highly elongated
complex structure. Under these conditions three distinct views could be
recognised (see Figure 11). Two views (interpreted as top-down/bottom-up)
show the Fab arms displaced clockwise or anti-clockwise as extensions of the
30   parallel plates with two-fold symmetry. The third view shows an image with
the two Fab arms in line roughly through the centre of the receptor on its
opposite sides, interpreted as a side projection of binding half-way up the
plates.

The use of aggressive uranyl stains operating at lower pHs revealed
35   internal structure of the molecular envelope at the expense of consistency of
the particle morphology. For example, staining with uranyl acetate or uranyl

formate showed that parallel bars can be seen in particles in which the Fab arms are displaced either clockwise or anticlockwise but not where the intermediate central or axial position of the two Fab arms is presented in projection. These observations show 83-7 MFab binding roughly half-way up

5   the side-edge of each hIR -11 ectodomain plate. The epitope recognised by Mab 83-7 has been mapped to the cys-rich region, residues 191-297, by analysis of chimeric receptors (Zhang and Roth, 1991, *Proc. Natl. Acad. Sci. USA* **88**, 9858-9862).

Imaging of hIR -11 ectodomain complexed with either 83-14 MFab or 18-44

10   **MFab**

Complexes were formed with Fabs from the most insulin-mimetic antibody Mab 83-14. Projections showing the Fab arms bound to and extending out from near the base of the U-shaped particles were identified. A second field of particles showed objects composed of two parallel bars as

15   observed for the undecorated ectodomain, with Fab arms projecting obliquely from diametrically opposite extremities (see Figure 11). Similar but less definitive images were also seen when MFab 18-44 was bound to hIR -11 ectodomain. The epitope for Mab 83-14 is between residues 469-592 (Prigent et al., 1990) in the connecting domain. This domain contains one of the

20   disulphide bonds (Cys524-Cys524) between the two monomers in the IR dimer (Schaffer and Ljungqvist, 1992, *Biochem. Biophys. Res. Commun.* **189**, 650-653). The epitope for Mab 18-44 is a linear epitope, residues 765-770 (Prigent et al., 1990, . *J. Biol. Chem.* **265**, 9970-9977) in the β-chain, near the end of the insert domain (O'Bryan et al., 1991, *Mol. Cell. Biol.* **11**, 5016-

25   5031). The insert domain contains the second disulphide bond connecting the two monomers in the IR dimer (Sparrow et al., 1997, *J. Biol. Chem.,* 272, 29460-29467).

Imaging of hIR -11 ectodomain co-complexed with two different MFabs per monomer

30   The double complex of hIR -11 ectodomain with MFabs 83-7 and 18-44 was stained with 2% KPT at pH 6.0, and revealed the molecular envelopes. The particle appears complex in shape, and can assume a number of different orientations on the carbon support film, giving rise to a number of different projections in the micrograph. The predominant view is of an

35   asymmetric X-shape (some examples circled). It shows the 83-7 MFab arms bound at opposite ends of the parallel bars with the two 18-44 MFabs

appearing as shorter projections extending out from either side of each ectodomain.

Images of the double complex of hIR -11 ectodomain with 83-7 and 83-14 MFabs gave X-shaped images similar to those seen with the 83-7/18-44
5   double complex. In contrast the double complex of hIR -11 ectodomain with 18-44 and 83-14 MFabs did not present the characteristic asymmetric X-shapes described above. Instead, the molecular envelope appeared to be elongated in many views, with only an occasional X-shaped projection. While a detailed interpretation of these images would be premature, it is
10 clear that MFabs 18-44 and 83-14, two of the more potent insulin mimetic antibodies (Prigent et al., 1990, *J. Biol. Chem.* **265**, 9970-9977), can bind simultaneously to the receptor.

Imaging of hIR -11 ectodomain co-complexed with three different MFabs per monomer

15   A field of particles from a micrograph of hIR -11 ectodomain were complexed simultaneously with MFabs 83-7, 83-14 and 18-44. In the thicker stain regions the molecular envelope was X-shaped, and looked very similar to that of the double complexes of hIR -11 ectodomain with either 83-7 and 18-44 or 83-7 and 83-14. However, in the more thinly stained regions
20 particles of greater complexity were visible, and it was possible occasionally to identify that there are in fact more than four MFabs bound to the ectodomain dimer.

The single-molecule imaging of hIR -11 ectodomain presented here suggests a molecular envelope for this dimeric species significantly different
25 from that of any previously published study. However, an unequivocal determination of the molecular envelope even from the present study is not entirely straightforward. A major complicating factor here has been the relative fragility of the expressed ectodomain when exposed to the rigors of electron microscope preparation by negative staining. For example, staining
30 with potassium phosphotungstate (KPT, pH 6.0-7.0) frequently suggested a denaturation of the dimeric molecules, but when appropriate conditions were satisfied, good seemingly interpretable molecular envelope images were achieved; staining with methylamine tungstate (pH ~7.0) supported the best KPT molecular envelope images, but had the suggestion of a swelling of the
35 molecular structure at neutral pH; and the acid-pH stains of uranyl acetate (pH ~4.2) and uranyl formate (pH~3.0), with their ability to penetrate the

ectodomain structure, appeared to illuminate not so much the molecular envelope as the zones of high projected protein density within the dimer.

An amalgam of impressions from these various staining regimens has led to the following interpretation of single-molecule images of these
5   undecorated, or naked, dimers: the predominant dimeric molecular image encountered here has been that of "parallel bars"of projected protein density. This view is so predominant, indeed, that it suggests there is either a single preferred orientation of the molecules on the glow-discharged carbon support film, or that this impression of parallel bars of density may represent a
10   mixture of superficially similar structure projections, with the subtleties of these different projections being masked by the relatively coarse resolution of this single-molecule direct imaging. The impression of parallel bars of projected protein density is particularly predominant in regions of thicker negative stain. A second view of the molecular envelope, appreciably less
15   well represented in regions of thicker stain but predominant in regions of thin staining, is that of 'open' U's, or V's. These two views of hIR -11 ectodomain were supported by the single-molecule imaging of hIGF-1R ectodomain under comparable conditions of negative staining.

If the assumption is made that these two recognisable projected
20   views, that of parallel bars and of open U's/V's, are different views of the same dimeric molecule, an assumption strongly supported by the MFab complex imaging, a coarse model of the molecular envelope can be rationalized. The model structure is roughly that of a cube, composed of two almost-parallel plates of high protein density, separated by a deep cleft of low
25   protein main-chain and side-chain density able to be penetrated by stain, and connected by intermediate stain-excluding density near what is assumed here to be their base (that is, nearest the membrane-anchoring region). The width of the low-density cleft appears to be of the order of 30-35Å, sufficient to accommodate the binding of the insulin molecule of diameter ca. 30Å,
30   although we have no electron microscopical evidence to support insulin-binding in this cleft at this stage.

It has been established through imaging of bound 83-7 MFab that there is a dimeric two-fold axis normal to the membrane surface between these plates of density. Occasionally, dimer images display a relative
35   displacement of the bars of density, interpreted here as a limited capacity for a shearing of the interconnecting zone between the two plates along their

horizontal axis parallel to the membrane; other images show bars skewed from parallel, implying a limited capacity for the plates to rotate independently around the two-fold axis, again via this interconnecting zone. These two observations each suggest a relatively flexible connectivity

5   between the dimer plates in the membrane-proximal region of intermediate protein density, which could possibly contribute to the transmembrane signalling process.

The approximate overall measured dimensions of the ectodomain dimer are 110 x 90 x 120Å, calibrated against the dimensions of imaged

10   influenza neuraminidase heads, known from the solved X-ray structure (Varghese et al., 1983, *Nature* **303**, 35-40). It can be noted that there is a compatibility here between the molecular weights and molecular dimensions of these two molecular species: the compact tetrameric influenza neuraminidase heads of Mr ~200 kDa occupy a volume almost 100 x 100 x

15   60 Å; the more open dimeric insulin receptor ectodomains of similar Mr ~240 kDa imaged here occupy a volume approximately 110 x 90 x 120 Å , roughly twice that of the neuraminidase heads, accommodating the slightly higher molecular weight and substantial central low-density cleft.

The low-resolution roughly cubic compact structure proposed here

20   differs substantially from the T-shaped model proposed by Christiansen et al. (1991, *Proc. Natl. Acad. Sci. U. S. A.* **88**, 249-252) and Tranum-Jensen et al., (1994, *J. Membrane Biol.* **140**, 215-223) for the whole receptor and the elongated model proposed by Schaefer et al. (1992, *J. Biol. Chem.* **267**, 23393-23402) for soluble ectodomain. Significantly, those previous studies did not

25   provide any convincing independent electron microscopical evidence that their imaged objects were in fact insulin receptor.

In the present study, the identity of the imaged molecules as   hIR -11 ectodomain has been confirmed by imaging complexes of the dimer with Fabs of the three well-established conformational Mabs against native hIR,

30   83-7, 83-14 and 18-44 (Soos et al.,1986, *Biochem. J.* **235**, 199-208; 1989, *Proc. Natl Acad. Sci. USA* **86**, 5217-5221), bound singly and in combination. In all these instances, virtually every particle in the field of view exhibited MFab decoration through binding to conformational epitopes, establishing not only the identity of the imaged particles but also the conformational integrity of

35   the expressed ectodomains. Furthermore, the cleanliness and uniformity of these hIR -11 ectodomain preparations, both naked and decorated, visualised

here by electron microscopy demonstrate their high suitability for X-ray crystallization trials.

The known flexibility of the Fab arms exacerbates image-to-image variability beyond the limited extent already described for the undecorated dimeric ectodomains, complicating any precise interpretation of these antigen-antibody complexes. Such molecular flexibility also renders largely impractical any single-molecule computer image averaging to facilitate image interpretation, progressively more so with the higher order antigen-antibody complexes studied here.

The most readily interpretable of these images, showing least image-to-image variability, are those of 83-7 MFab bound to dimers where, fortuitously, the antigen-antibody complex is constrained in its degrees of rotational freedom on the carbon support film. Many projected images show the two Fab arms in line roughly through the centre of the antigen on its opposite sides, interpreted as a side projection of binding half-way up the plates from their membrane-proximal base. Other sub-sets of images show the two Fab arms still parallel but displaced clockwise or anticlockwise with 2-fold symmetry, each Fab approximating an extension of one of the parallel bars of antigen density, interpreted here as representing top or bottom projections along the 2-fold axis. The third projection, along the axis of the Fab arms, could not be sampled here because of the constraining geometry of this molecular complex. These observations suggest binding of 83-7 MFab roughly half-way up the side-edge of the hIR -11 ectodomain plate. This then allows an initial attempt at spatially mapping the 83-7 MFab epitope, which has been sequence-mapped to residues 191-297 in the cys-rich region of the insulin receptor (Zhang and Roth, 1991, *Proc. Natl. Acad. Sci. USA* **88**, 9858-9862). The spatial separation and relative orientations of the two binding epitopes of Mab 83-7 on the hIR -11 ectodomain dimer as indicated here appear inconsistent with the proposal that Mab 83-7 could bind intramolecularly to hIR (O'Brien et al., 1987, *Biochem J.* **6**, 4003-4010).

Decoration of the ectodomain dimer with 83-7 MFab established that the two plates of high protein-density are arranged with 2-fold symmetry. Decoration with either 83-14 or 18-44 MFab, on the other hand, allowed sampling of the third projection of the ectodomain dimer precluded by 83-7 MFab binding. Significantly, this third view established unequivocally the U-shaped projection of the hIR -11 ectodomain dimer, something which was

only able to be assumed with the undecorated ectodomain images. Further, this projection has allowed a rough spatial mapping close to the base of the U-shaped dimer for the epitopes recognised by 83-14 MFab (residues 469-592, connecting domain) and 18-44 MFab (residues 765-770, b-chain insert

5   domain; exon 11 plus numbering, Prigent et al., 1990, *J. Biol. Chem.* **265**, 9970-9977).

Inherent in the model structure is the implication that, with the two-fold axis aligned normal to the membrane surface, the mouth of the low-density cleft where insulin binding may occur would lie most distant from

10   the transmembrane anchor, whilst the zone of intermediate density connecting the two high-density plates would be in close proximity to the membrane. It follows, in this model, that the L1/cys-rich/L2 domains(Bajaj et al., 1997, *Biochim. Biophys. Acta* **916**, 220-226; Ward et al.,1995, *Proteins: Struct., Funct., Genet.* **22**, 141-153), which comprise much of the insulin-

15   binding region (see Mynarcik et al., 1997, . *J. Biol. Chem.* **272**, 2077-2081), most probably lie in the membrane-distal upper halves of the two plates, whilst the membrane-proximal lower halves contain the connecting domains, the fibronectin-type domains, the insert domains and the interchain disulphide bonds (Schaffer and Ljungqvist, 1992, *Biochem. Biophys. Res.*

20   *Commun.* **189**, 650-653; Sparrow et al., 1997, *J. Biol. Chem.*, 272, 29460-29467). Such a disposition of domains is supported by the images seen with the single MFab decoration, the 83-7 MFab epitope in the cys-rich region being spatially mapped roughly half-way up the side-edge of the ectodomain plates, and the 83-14 and 18-44 MFab epitopes (connecting domain and β-

25   chain insert domain, respectively) being mapped near the base of the plates. Our preference is for a single a-bc monomer to occupy a single plate, although the possibility of a single monomer straddling the two plates of protein density cannot be discounted.

The more complex images involving co-binding of two, and even

30   more so of all three, MFabs to each monomer of the ectodomain dimer are not easily interpretable with respect to relative domain arrangements within the monomer at present, not least of all because of the difficulty of finding conditions of negative staining that will simultaneously maintain the integrity of the Fab binding while highlighting recognisable and

35   reproducible details of the internal structure of the dimeric IR ectodomain.

The data presented here demonstrate the ability of single-molecule imaging to give an initial insight into the topology of multidomain structures such as the ectodomain of hIR, and the value of combining this technique with that of either single or multiple monoclonal Fab attachment per monomer as a potential means of epitope, and domain, mapping of the structure. By imaging Fab complexes of other members of the family, such as hIGF-1R ectodomain, and combining available sequence-mapped epitope information with that presented here, a more comprehensive understanding of domain arrangements within the IR family ectodomains should be forthcoming.

EXAMPLE 5

Structure-Based Design of Ligands for the IGF Receptor as Potential Inhibitors of IGF Binding

The structure of IGF receptor can be considered as a filter or screen to design, or evaluate, potential ligands for the receptor. Those skilled in the art can use a number of well known methods for de novo ligand design, such as GRID, GREEN, HSITE, MCSS, HINT, BUCKETS, CLIX, LUDI, CAVEAT, SPLICE, HOOK, NEWLEAD, PRO_LIGAND, ELANA, LEGEND, GenStar, GrowMol, GROW, GEMINI, GroupBuild, SPROUT, and LEAPFROG, to generate potential agonists or antagonists for IGF-1R. In addition, the IGF-1R structure may be used as a query for database searches for potential ligands. The databases searched may be existing eg ACD, Cambridge Crystallographic, NCI, or virtual. Virtual databases, which contain very large numbers (currently up to 10^{12}) of chemically reasonable structures, may be generated by those skilled in the art using techniques such as DBMaker, ChemSpace, TRIAD and ILIAD.

The IGFR structure contains a number of sites into which putative ligands may bind. Search strategies known to those skilled in the art may be used to identify putative ligands for these sites. Examples of two suitable search strategies are described below:

(i)   *Database Search*

The properties of key parts of the putative site may be used as a database search query. For example, the Unity 2.x database software may be used. A flexible 3D search can be run in which a "directed tweak" algorithm is used to find low energy conformations of potential ligands which satisfy the query.

(ii)   *De novo design of ligands*

The Leapfrog algorithm as incorporated in the software package, Sybyl version 6.4.2 (Tripos Associates, St Louis), may be used to design potential ligands for IGF-1R sites. The coordinates of residues around the site may be taken from the x-ray structure, hydrogens and charges (Kollman all atom

5   dictionary charges) added. From the size, shape and properties of the site, a number of potential ligands may be proposed. Leapfrog may be used to optimize the conformation of ligands and position on the site, to rank the likely strength of binding interactions with IGF-1R, and to suggest modifications to the structures which would have enhanced binding.

10   It is also possible to design ligands capable of interacting with more than one site. One way in which this may be done is by attaching flexible linkers to ligands designed for specific sites so as to join them. The linkers may be attached in such a way that they do not disrupt the binding to individual sites.

15   All references cited above are incorporated herein in their entirety by reference.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the

20   invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Claims:

1.   A method of designing a compound able to bind to a molecule of the
insulin receptor family and to modulate an activity mediated by the molecule,
5   including the step of assessing the stereochemical complementarity between the
compound and the receptor site of the molecule, wherein the receptor site
includes:

(a)   amino acids 1 to 462 of the receptor for IGF-1, having the atomic
coordinates substantially as shown in Figure 1;

10   (b)   a subset of said amino acids, or;

(c)   amino acids present in the amino acid sequence of a member of the
insulin receptor family, which form an equivalent three-dimensional structure to
that of the receptor molecule as depicted in Figure 1.

15   2.   A method according to claim 1, in which the compound is selected or
modified from a known compound identified from a database.

3.   A method according to claim 1, in which the compound is designed so
as to complement the structure of the receptor molecule as depicted in Figure 1.

20

4.   A method according to any one of claims 1 to 3, in which the compound
has structural regions able to make close contact with amino acid residues at the
surface of the receptor site lining the groove, as depicted in Figure 2.

25   5.   A method according to any one of claims 1 to 4, in which the compound
has a stereochemistry such that it can interact with both the L1 and L2 domains
of the receptor site.

6.   A method according to any one of claims 1 to 4, in which the compound
30   has a stereochemistry such that it can interact with the L1 domain of a first
monomer of the receptor homodimer, and with the L2 domain of the other
monomer of the receptor homodimer.

7.   A method according to any one of claims 1 to 4, in which the interaction
35   of the compound with the receptor site alters the position of at least one of the

L1, L2 or cysteine-rich domains of the receptor molecule relative to the position of at least one of the other of said domains.

8.   A method according to claim 7, in which the compound interacts with the β sheet of the L1 domain of the receptor molecule, thereby causing an alteration in the position of the L1 domain relative to the position of the cysteine-rich domain or of the L2 domain.

9.   A method according to claim 7, in which the compound interacts with the receptor site in the region of the interface between the L1 domain an the cysteine-rich domain of the receptor molecule, thereby causing the L1 domain and the cysteine-rich domain to move away from each other.

10.   A method according to claim 7, in which the compound interacts with the hinge region between the L2 domain and the cysteine-rich domain of the receptor molecule, thereby causing an alteration in the positions of the L2 domain and the cysteine-rich domain relative to each other.

11.   A method according to any one of claims 1 to 10, in which the stereochemical complementarity between the compound and the receptor site is such that the compound has a K_b for the receptor side of less than 10^{-6}M.

12.   A method according to claim 11, in which the K_b is less than 10^{-8}M.

13.   A method according to any one of claims 1 to 12, in which the compound has the ability to increase an activity mediated by the receptor molecule.

14.   A method according to any one of claims 1 to 12, in which the compound has the ability to decrease an activity mediated by the receptor molecule.

15.   A method according to claim 14, in which the stereochemical interaction between the compound and the receptor site is adapted to prevent the binding of a natural ligand of the receptor molecule to the receptor site.

16.   A method according to claim 14 or claim 15, in which the compound has a K_1 of less than $10^{-6}M$.

17.   A method according to claim 16, in which the compound has a K_1 of less than $10^{-8}M$.

18.   A method according to claim 17, in which the compound has a K_1 of less than $10^{-9}M$.

19.   A method according to any one of claims 1 to 18, in which the receptor is the IGF-1R.

20.   A method according to any one of claims 1 to 18, in which the receptor is the insulin receptor.

21.   A computer-assisted method for identifying potential compounds able to bind to a molecule of the insulin receptor family and to modulate an activity mediated by the molecule, using a programmed computer including a processor, an input device, and an output device, including the steps of:

     (a)   inputting into the programmed computer, through the input device, data comprising the atomic coordinates of the IGF-1R molecule as shown in Figure 1, or a subset thereof;

     (b)   generating, using computer methods, a set of atomic coordinates of a structure that possesses stereochemical complementarity to the atomic coordinates of the IGF-1R site as shown in Figure 1, or a subset thereof, thereby generating a criteria data set;

     (c)   comparing, using the processor, the criteria data set to a computer database of chemical structures;

     (d)   selecting from the database, using computer methods, chemical structures which are structurally similar to a portion of said criteria data set; and

     (e)   outputting, to the output device, the selected chemical structures which are similar to a portion of the criteria data set.

22.   A computer-assisted method according to claim 21, in which the method is used to identify potential compounds which have the ability to decrease an activity mediated by the receptor.

23.   A computer-assisted method according to claim 21 or claim 22, which further includes the step of selecting one or more chemical structures from step (e) which interact with the receptor site of the molecule in a manner which prevents the binding of natural ligands to the receptor site.

24.   A computer-assisted method according to any one of claims 21 to 23, which further includes the step of obtaining a compound with a chemical structure selected in steps (d) and (e), and testing the compound for the ability to decrease an activity mediated by the receptor.

25.   A computer-assisted method according to claim 21, in which the method is used to identify potential compounds which have the ability to increase an activity mediated by the receptor molecule.

26.   A computer-assisted method according to claim 25, further including the step of obtaining a molecule with a chemical structure selected in steps (d) and (e), and testing the compound for the ability to increase an activity mediated by the receptor.

27.   A computer-assisted method according to any one of claims 21 to 26, in which the receptor is the IGF-1R.

28.   A computer-assisted method according to any one of claims 21 to 26, in which the receptor is the insulin receptor.

29.   A method of screening of a putative compound having the ability to modulate the activity of a receptor of the insulin receptor family, including the steps of identifying a putative compound by a method according to any one of claims 1 to 29, and testing the compound for the ability to increase or decrease an activity mediated by the receptor.

30.   A method according to claim 29, in which the test is carried out *in vitro*.

31.   A method according to claim 29, in which the test is a high throughput assay.

32. A method according to claim 29, in which the test is carried out *in vivo*.

33. A method according to claim 30, in which the test is carried out *in vivo*.

5

Figure 1

ATOM	1	CB	GLU	1	55.907	11.986	66.300	1.00	59.11	AAAA	C
ATOM	2	CG	GLU	1	56.138	11.019	65.162	1.00	79.17	AAAA	C
ATOM	3	CD	GLU	1	57.382	11.319	64.321	1.00	85.10	AAAA	C
ATOM	4	OE1	GLU	1	58.404	10.754	64.795	1.00	86.18	AAAA	O
ATOM	5	OE2	GLU	1	57.424	12.013	63.270	1.00	78.70	AAAA	O
ATOM	6	C	GLU	1	53.508	12.557	66.350	1.00	48.46	AAAA	C
ATOM	7	O	GLU	1	52.685	11.863	65.784	1.00	51.27	AAAA	O
ATOM	10	H	GLU	1	54.256	10.338	67.159	1.00	61.64	AAAA	H
ATOM	12	CA	GLU	1	54.602	11.778	67.081	1.00	54.77	AAAA	C
ATOM	13	H	ILE	2	53.608	13.860	66.375	1.00	37.66	AAAA	H
ATOM	15	CA	ILE	2	52.768	14.699	65.604	1.00	40.87	AAAA	C
ATOM	16	CB	ILE	2	52.925	16.122	66.160	1.00	41.97	AAAA	C
ATOM	17	CG2	ILE	2	52.036	17.122	65.484	1.00	38.50	AAAA	C
ATOM	18	CG1	ILE	2	52.560	16.006	67.663	1.00	46.58	AAAA	C
ATOM	19	CD1	ILE	2	53.150	17.176	68.498	1.00	32.29	AAAA	C
ATOM	20	C	ILE	2	53.122	14.711	64.139	1.00	46.47	AAAA	C
ATOM	21	O	ILE	2	54.258	15.029	63.852	1.00	51.65	AAAA	O
ATOM	22	H	CYS	3	52.235	14.409	63.196	1.00	49.61	AAAA	H
ATOM	24	CA	CYS	3	52.435	14.677	61.773	1.00	38.93	AAAA	C
ATOM	25	C	CYS	3	51.429	15.708	61.302	1.00	42.06	AAAA	C
ATOM	26	O	CYS	3	50.290	15.521	61.690	1.00	42.37	AAAA	O
ATOM	27	CB	CYS	3	52.159	13.415	60.999	1.00	35.66	AAAA	C
ATOM	28	SG	CYS	3	53.019	12.004	61.674	1.00	36.98	AAAA	S
ATOM	29	H	GLY	4	51.851	16.709	60.580	1.00	42.39	AAAA	H
ATOM	31	CA	GLY	4	50.973	17.718	60.003	1.00	47.71	AAAA	C
ATOM	32	C	GLY	4	51.703	18.407	58.869	1.00	48.23	AAAA	C
ATOM	33	O	GLY	4	52.916	18.345	58.884	1.00	55.36	AAAA	O
ATOM	34	N	PRO	5	51.056	19.212	58.048	1.00	49.63	AAAA	H
ATOM	35	CD	PRO	5	51.637	19.947	56.860	1.00	45.28	AAAA	C
ATOM	36	CA	PRO	5	49.605	19.341	58.083	1.00	41.57	AAAA	C
ATOM	37	CB	PRO	5	49.397	20.703	57.474	1.00	44.30	AAAA	C
ATOM	38	CG	PRO	5	50.632	21.036	56.683	1.00	46.43	AAAA	C
ATOM	39	C	PRO	5	48.932	18.217	57.354	1.00	36.40	AAAA	C
ATOM	40	O	PRO	5	49.403	17.094	57.396	1.00	43.35	AAAA	O
ATOM	41	H	GLY	6	47.787	18.438	56.795	1.00	39.15	AAAA	H
ATOM	43	CA	GLY	6	46.896	17.336	56.350	1.00	39.24	AAAA	C
ATOM	44	C	GLY	6	47.710	16.365	55.529	1.00	33.68	AAAA	C
ATOM	45	O	GLY	6	48.510	16.863	54.753	1.00	36.00	AAAA	O
ATOM	46	H	ILE	7	47.586	15.111	55.788	1.00	35.70	AAAA	N
ATOM	48	CA	ILE	7	48.307	14.053	55.141	1.00	37.65	AAAA	C
ATOM	49	CB	ILE	7	48.556	12.797	55.933	1.00	36.31	AAAA	C
ATOM	50	CG2	ILE	7	49.043	11.700	54.988	1.00	34.67	AAAA	C
ATOM	51	CG1	ILE	7	49.561	12.857	57.067	1.00	39.34	AAAA	C
ATOM	52	CD1	ILE	7	49.678	14.249	57.668	1.00	40.22	AAAA	C
ATOM	53	C	ILE	7	47.338	13.762	53.977	1.00	45.00	AAAA	C
ATOM	54	O	ILE	7	46.150	13.843	54.195	1.00	51.52	AAAA	O
ATOM	55	H	ASP	8	47.767	13.631	52.751	1.00	45.60	AAAA	H
ATOM	57	CA	ASP	8	46.938	13.283	51.631	1.00	44.05	AAAA	C
ATOM	58	CB	ASP	8	47.003	14.469	50.651	1.00	44.21	AAAA	C
ATOM	59	CG	ASP	8	45.909	14.379	49.600	1.00	43.48	AAAA	C
ATOM	60	OD1	ASP	8	45.660	13.262	49.096	1.00	51.77	AAAA	O
ATOM	61	OD2	ASP	8	45.253	15.374	49.251	1.00	46.84	AAAA	O
ATOM	62	C	ASP	8	47.428	12.000	50.992	1.00	42.16	AAAA	C
ATOM	63	O	ASP	8	48.423	12.143	50.330	1.00	48.50	AAAA	O
ATOM	64	H	ILE	9	47.096	10.817	51.321	1.00	42.76	AAAA	H
ATOM	66	CA	ILE	9	47.441	9.505	50.939	1.00	44.05	AAAA	C
ATOM	67	CB	ILE	9	47.212	8.483	52.077	1.00	40.82	AAAA	C
ATOM	68	CG2	ILE	9	47.669	7.085	51.653	1.00	36.35	AAAA	C
ATOM	69	CG1	ILE	9	47.888	8.917	53.364	1.00	41.17	AAAA	C
ATOM	70	CD1	ILE	9	49.376	8.947	53.286	1.00	43.78	AAAA	C
ATOM	71	C	ILE	9	46.530	9.137	49.794	1.00	51.48	AAAA	C
ATOM	72	O	ILE	9	45.338	9.420	49.832	1.00	63.05	AAAA	O
ATOM	73	H	ARG	10	47.004	8.417	48.812	1.00	54.87	AAAA	N
ATOM	75	CA	ARG	10	46.283	8.089	47.600	1.00	54.17	AAAA	C
ATOM	76	CB	ARG	10	45.703	9.358	47.023	1.00	48.54	AAAA	C
ATOM	77	CG	ARG	10	46.361	10.169	45.952	1.00	46.55	AAAA	C
ATOM	78	CD	ARG	10	46.002	11.635	46.264	1.00	52.63	AAAA	C
ATOM	79	HE	ARG	10	45.082	12.326	45.284	1.00	59.27	AAAA	H
ATOM	81	CZ	ARG	10	44.269	13.262	45.498	1.00	56.22	AAAA	C
ATOM	82	HH1	ARG	10	44.153	13.891	46.666	1.00	55.14	AAAA	H
ATOM	85	HH2	ARG	10	43.455	13.803	44.602	1.00	52.29	AAAA	H
ATOM	88	C	ARG	10	47.019	7.373	46.492	1.00	57.23	AAAA	C
ATOM	89	O	ARG	10	48.240	7.288	46.281	1.00	56.32	AAAA	O
ATOM	90	H	ASN	11	46.248	6.654	45.629	1.00	57.23	AAAA	H
ATOM	92	CA	ASN	11	46.800	5.917	44.494	1.00	50.73	AAAA	C
ATOM	93	CB	ASN	11	47.704	6.798	43.671	1.00	44.65	AAAA	C
ATOM	94	CG	ASN	11	46.878	7.732	42.829	1.00	50.72	AAAA	C
ATOM	95	OD1	ASN	11	45.749	7.451	42.403	1.00	72.59	AAAA	O
ATOM	96	HD2	ASN	11	47.499	8.869	42.587	1.00	54.38	AAAA	H
ATOM	99	C	ASN	11	47.635	4.736	44.915	1.00	53.07	AAAA	C
ATOM	100	O	ASN	11	47.303	3.701	44.347	1.00	51.95	AAAA	O
ATOM	101	H	ASP	12	48.569	4.822	45.878	1.00	50.96	AAAA	H
ATOM	103	CA	ASP	12	49.204	3.570	46.263	1.00	55.44	AAAA	C

ATOM	104	CB	ASP	12	50.668	3.568	45.758	1.00 66.47	AAAA C
ATOM	105	CG	ASP	12	50.879	4.026	44.314	1.00 68.25	AAAA C
ATOM	106	OD1	ASP	12	50.441	3.185	43.457	1.00 58.31	AAAA O
ATOM	107	OD2	ASP	12	51.391	5.120	43.989	1.00 70.56	AAAA O
ATOM	108	C	ASP	12	49.061	3.322	47.758	1.00 59.23	AAAA C
ATOM	109	O	ASP	12	49.687	3.849	48.711	1.00 59.65	AAAA O
ATOM	110	N	TYR	13	48.411	2.187	48.036	1.00 59.64	AAAA N
ATOM	112	CA	TYR	13	48.328	1.672	49.397	1.00 64.06	AAAA C
ATOM	113	CB	TYR	13	47.968	0.196	49.409	1.00 64.56	AAAA C
ATOM	114	CG	TYR	13	47.467	-0.357	50.721	1.00 69.18	AAAA C
ATOM	115	CD1	TYR	13	46.216	-0.024	51.248	1.00 72.71	AAAA C
ATOM	116	CE1	TYR	13	45.746	-0.541	52.450	1.00 71.51	AAAA C
ATOM	117	CD2	TYR	13	48.233	-1.247	51.457	1.00 70.36	AAAA C
ATOM	118	CE2	TYR	13	47.788	-1.778	52.661	1.00 71.64	AAAA C
ATOM	119	CZ	TYR	13	46.542	-1.420	53.160	1.00 71.31	AAAA C
ATOM	120	OH	TYR	13	46.144	-1.977	54.358	1.00 63.25	AAAA O
ATOM	122	C	TYR	13	49.622	1.839	50.198	1.00 65.99	AAAA C
ATOM	123	O	TYR	13	49.621	2.321	51.354	1.00 65.01	AAAA O
ATOM	124	N	GLN	14	50.786	1.541	49.594	1.00 63.51	AAAA N
ATOM	126	CA	GLN	14	52.078	1.681	50.218	1.00 63.51	AAAA C
ATOM	127	CB	GLN	14	53.174	1.318	49.219	1.00 68.37	AAAA C
ATOM	128	CG	GLN	14	52.963	-0.078	48.686	1.00 84.62	AAAA C
ATOM	129	CD	GLN	14	53.990	-0.515	47.754	1.00 92.28	AAAA C
ATOM	130	OE1	GLN	14	53.945	-0.161	46.573	1.00 94.82	AAAA O
ATOM	131	NE2	GLN	14	54.920	-1.254	48.361	1.00 98.03	AAAA N
ATOM	134	C	GLN	14	52.434	3.058	50.753	1.00 61.62	AAAA C
ATOM	135	O	GLN	14	53.266	3.292	51.644	1.00 62.09	AAAA O
ATOM	136	N	GLN	15	51.628	4.038	50.349	1.00 57.02	AAAA N
ATOM	138	CA	GLN	15	51.724	5.399	50.831	1.00 51.71	AAAA C
ATOM	139	CB	GLN	15	50.861	6.220	49.911	1.00 43.75	AAAA C
ATOM	140	CG	GLN	15	51.566	6.605	48.648	1.00 59.65	AAAA C
ATOM	141	CD	GLN	15	51.554	8.105	48.428	1.00 72.96	AAAA C
ATOM	142	OE1	GLN	15	51.168	9.005	49.184	1.00 80.58	AAAA O
ATOM	143	NE2	GLN	15	52.016	8.378	47.211	1.00 74.17	AAAA N
ATOM	146	C	GLN	15	51.219	5.530	52.258	1.00 50.15	AAAA C
ATOM	147	O	GLN	15	51.576	6.500	52.940	1.00 48.04	AAAA O
ATOM	148	N	LEU	16	50.440	4.535	52.688	1.00 46.22	AAAA N
ATOM	150	CA	LEU	16	49.913	4.449	54.019	1.00 45.52	AAAA C
ATOM	151	CB	LEU	16	48.950	3.295	54.159	1.00 37.73	AAAA C
ATOM	152	CG	LEU	16	47.502	3.425	53.707	1.00 41.40	AAAA C
ATOM	153	CD1	LEU	16	46.837	2.063	53.790	1.00 42.43	AAAA C
ATOM	154	CD2	LEU	16	46.687	4.424	54.545	1.00 35.93	AAAA C
ATOM	155	C	LEU	16	51.042	4.280	55.039	1.00 51.52	AAAA C
ATOM	156	O	LEU	16	50.913	4.601	56.235	1.00 52.53	AAAA O
ATOM	157	N	LYS	17	52.252	3.936	54.560	1.00 51.01	AAAA N
ATOM	159	CA	LYS	17	53.422	3.914	55.404	1.00 50.73	AAAA C
ATOM	160	CB	LYS	17	54.609	3.252	54.737	1.00 56.10	AAAA C
ATOM	161	CG	LYS	17	54.539	1.733	54.831	1.00 62.40	AAAA C
ATOM	162	CD	LYS	17	54.768	1.278	53.387	1.00 63.85	AAAA C
ATOM	163	CE	LYS	17	55.316	-0.141	53.426	1.00 68.40	AAAA C
ATOM	164	NZ	LYS	17	56.537	-0.225	52.554	1.00 73.83	AAAA N
ATOM	168	C	LYS	17	53.944	5.270	55.852	1.00 44.78	AAAA C
ATOM	169	O	LYS	17	54.492	5.262	56.933	1.00 39.39	AAAA O
ATOM	170	N	ARG	18	53.524	6.344	55.201	1.00 41.15	AAAA N
ATOM	172	CA	ARG	18	53.827	7.673	55.676	1.00 43.01	AAAA C
ATOM	173	CB	ARG	18	53.250	8.702	54.704	1.00 43.97	AAAA C
ATOM	174	CG	ARG	18	53.888	8.764	53.333	1.00 53.60	AAAA C
ATOM	175	CD	ARG	18	52.964	9.362	52.269	1.00 60.34	AAAA C
ATOM	176	NE	ARG	18	52.528	10.703	52.650	1.00 50.00	AAAA N
ATOM	178	CZ	ARG	18	51.628	11.444	52.021	1.00 48.86	AAAA C
ATOM	179	NH1	ARG	18	51.068	10.941	50.943	1.00 47.96	AAAA N
ATOM	182	NH2	ARG	18	51.377	12.656	52.555	1.00 43.72	AAAA N
ATOM	185	C	ARG	18	53.238	7.924	57.077	1.00 44.03	AAAA C
ATOM	186	O	ARG	18	53.402	9.010	57.644	1.00 45.53	AAAA O
ATOM	187	N	LEU	19	52.445	7.069	57.632	1.00 46.36	AAAA N
ATOM	189	CA	LEU	19	51.653	7.282	58.794	1.00 50.25	AAAA C
ATOM	190	CB	LEU	19	50.196	6.924	58.674	1.00 50.83	AAAA C
ATOM	191	CG	LEU	19	49.202	7.371	57.608	1.00 46.43	AAAA C
ATOM	192	CD1	LEU	19	47.946	6.743	57.852	1.00 22.57	AAAA C
ATOM	193	CD2	LEU	19	49.018	8.866	57.495	1.00 45.88	AAAA C
ATOM	194	C	LEU	19	52.210	6.428	59.912	1.00 49.87	AAAA C
ATOM	195	O	LEU	19	51.970	6.810	61.030	1.00 51.54	AAAA O
ATOM	196	N	GLU	20	53.270	5.708	59.652	1.00 49.35	AAAA N
ATOM	198	CA	GLU	20	53.819	4.833	60.679	1.00 49.60	AAAA C
ATOM	199	CB	GLU	20	54.876	3.960	59.982	1.00 57.91	AAAA C
ATOM	200	CG	GLU	20	55.893	4.840	59.272	1.00 70.16	AAAA C
ATOM	201	CD	GLU	20	57.095	4.077	58.757	1.00 69.35	AAAA C
ATOM	202	OE1	GLU	20	58.123	4.795	58.722	1.00 71.38	AAAA O
ATOM	203	OE2	GLU	20	56.993	2.885	58.420	1.00 72.84	AAAA O
ATOM	204	C	GLU	20	54.310	5.417	61.989	1.00 43.55	AAAA C
ATOM	205	O	GLU	20	54.301	4.652	62.937	1.00 40.01	AAAA O
ATOM	206	N	ASN	21	54.833	6.659	62.207	1.00 41.06	AAAA N
ATOM	208	CA	ASN	21	55.054	7.204	63.454	1.00 47.17	AAAA C
ATOM	209	C	ASN	21	54.066	8.141	64.108	1.00 49.76	AAAA C
ATOM	210	O	ASN	21	54.228	8.456	65.303	1.00 48.16	AAAA O

ATOM	211	CB	ASN	21	56.379	8.003	63.399	1.00	59.11	AAAA	C
ATOM	212	CG	ASN	21	57.413	7.951	62.796	1.00	68.38	AAAA	C
ATOM	213	OD1	ASN	21	57.499	8.855	63.122	1.00	58.51	AAAA	O
ATOM	214	ND2	ASN	21	58.348	7.469	61.890	1.00	77.00	AAAA	N
ATOM	216	N	CYS	22	53.129	8.711	63.351	1.00	47.44	AAAA	N
ATOM	218	CA	CYS	22	52.107	9.614	63.879	1.00	42.99	AAAA	C
ATOM	219	C	CYS	22	51.215	9.089	65.021	1.00	40.43	AAAA	C
ATOM	220	O	CYS	22	50.750	7.923	65.069	1.00	36.07	AAAA	O
ATOM	221	CB	CYS	22	51.182	9.921	62.690	1.00	44.82	AAAA	C
ATOM	222	SG	CYS	22	52.076	10.328	61.148	1.00	39.51	AAAA	S
ATOM	223	N	THR	23	51.287	9.801	66.137	1.00	36.24	AAAA	N
ATOM	225	CA	THR	23	50.339	9.482	67.204	1.00	43.51	AAAA	C
ATOM	226	CB	THR	23	50.944	9.481	68.593	1.00	41.38	AAAA	C
ATOM	227	OG1	THR	23	51.410	10.843	68.822	1.00	51.21	AAAA	O
ATOM	229	CG2	THR	23	52.110	8.571	68.838	1.00	33.83	AAAA	C
ATOM	230	C	THR	23	49.250	10.599	67.116	1.00	44.55	AAAA	C
ATOM	231	O	THR	23	48.085	10.414	67.481	1.00	45.95	AAAA	O
ATOM	232	N	VAL	24	49.646	11.797	66.689	1.00	33.03	AAAA	N
ATOM	234	CA	VAL	24	48.732	12.855	66.442	1.00	35.29	AAAA	C
ATOM	235	CB	VAL	24	48.925	13.979	67.456	1.00	30.60	AAAA	C
ATOM	236	CG1	VAL	24	48.056	15.157	67.082	1.00	27.21	AAAA	C
ATOM	237	CG2	VAL	24	48.656	13.566	68.886	1.00	25.37	AAAA	C
ATOM	238	C	VAL	24	48.895	13.447	65.043	1.00	41.52	AAAA	C
ATOM	239	O	VAL	24	49.987	13.963	64.791	1.00	44.40	AAAA	O
ATOM	240	N	ILE	25	47.855	13.450	64.203	1.00	40.13	AAAA	N
ATOM	242	CA	ILE	25	47.908	14.094	62.882	1.00	32.05	AAAA	C
ATOM	243	CB	ILE	25	47.113	13.299	61.853	1.00	25.85	AAAA	C
ATOM	244	CG2	ILE	25	47.027	14.039	60.542	1.00	18.73	AAAA	C
ATOM	245	CG1	ILE	25	47.677	11.896	61.705	1.00	29.80	AAAA	C
ATOM	246	CD1	ILE	25	47.169	11.155	60.471	1.00	27.41	AAAA	C
ATOM	247	C	ILE	25	47.397	15.490	62.941	1.00	32.92	AAAA	C
ATOM	248	O	ILE	25	46.223	15.776	63.213	1.00	40.91	AAAA	O
ATOM	249	N	GLU	26	48.264	16.472	63.042	1.00	36.60	AAAA	N
ATOM	251	CA	GLU	26	47.832	17.847	63.226	1.00	29.24	AAAA	C
ATOM	252	CB	GLU	26	48.875	18.703	63.856	1.00	29.92	AAAA	C
ATOM	253	CG	GLU	26	48.490	20.144	64.116	1.00	38.06	AAAA	C
ATOM	254	CD	GLU	26	49.561	20.762	65.013	1.00	37.39	AAAA	C
ATOM	255	OE1	GLU	26	50.654	20.937	64.489	1.00	41.56	AAAA	O
ATOM	256	OE2	GLU	26	49.571	21.175	66.182	1.00	49.16	AAAA	O
ATOM	257	C	GLU	26	47.413	18.376	61.869	1.00	37.79	AAAA	C
ATOM	258	O	GLU	26	48.161	19.069	61.181	1.00	39.68	AAAA	O
ATOM	259	N	GLY	27	46.117	18.104	61.582	1.00	37.28	AAAA	N
ATOM	261	CA	GLY	27	45.498	18.503	60.320	1.00	31.17	AAAA	C
ATOM	262	C	GLY	27	44.531	17.400	59.893	1.00	33.72	AAAA	C
ATOM	263	O	GLY	27	43.988	16.715	60.775	1.00	33.29	AAAA	O
ATOM	264	N	TYR	28	44.304	17.209	58.604	1.00	29.24	AAAA	N
ATOM	266	CA	TYR	28	43.318	16.189	58.253	1.00	28.93	AAAA	C
ATOM	267	CB	TYR	28	42.403	16.794	57.217	1.00	31.53	AAAA	C
ATOM	268	CG	TYR	28	43.058	17.256	55.962	1.00	31.78	AAAA	C
ATOM	269	CD1	TYR	28	43.704	16.355	55.116	1.00	36.07	AAAA	C
ATOM	270	CE1	TYR	28	44.361	16.706	53.967	1.00	28.91	AAAA	C
ATOM	271	CD2	TYR	28	43.130	18.572	55.606	1.00	30.98	AAAA	C
ATOM	272	CE2	TYR	28	43.769	18.972	54.428	1.00	28.77	AAAA	C
ATOM	273	CZ	TYR	28	44.367	18.021	53.652	1.00	31.53	AAAA	C
ATOM	274	OH	TYR	28	44.971	18.425	52.464	1.00	44.74	AAAA	O
ATOM	276	C	TYR	28	43.953	14.946	57.697	1.00	29.23	AAAA	C
ATOM	277	O	TYR	28	45.119	15.147	57.383	1.00	35.58	AAAA	O
ATOM	278	N	LEU	29	43.250	13.900	57.445	1.00	26.63	AAAA	N
ATOM	280	CA	LEU	29	43.764	12.730	56.803	1.00	29.83	AAAA	C
ATOM	281	CB	LEU	29	43.830	11.611	57.856	1.00	27.09	AAAA	C
ATOM	282	CG	LEU	29	44.212	10.258	57.242	1.00	31.90	AAAA	C
ATOM	283	CD1	LEU	29	45.538	10.396	56.469	1.00	35.03	AAAA	C
ATOM	284	CD2	LEU	29	44.551	9.203	58.290	1.00	25.05	AAAA	C
ATOM	285	C	LEU	29	42.897	12.342	55.616	1.00	33.84	AAAA	C
ATOM	286	O	LEU	29	41.689	12.165	55.806	1.00	43.23	AAAA	O
ATOM	287	N	HIS	30	43.389	12.385	54.395	1.00	35.95	AAAA	N
ATOM	289	CA	HIS	30	42.681	11.891	53.197	1.00	34.92	AAAA	C
ATOM	290	CB	HIS	30	42.893	12.801	52.027	1.00	32.85	AAAA	C
ATOM	291	CG	HIS	30	42.372	14.155	52.046	1.00	25.08	AAAA	C
ATOM	292	CD2	HIS	30	41.519	14.753	52.907	1.00	40.88	AAAA	C
ATOM	293	ND1	HIS	30	42.717	15.120	51.128	1.00	33.66	AAAA	N
ATOM	295	CE1	HIS	30	42.080	16.281	51.444	1.00	31.33	AAAA	C
ATOM	296	NE2	HIS	30	41.329	16.093	52.539	1.00	37.27	AAAA	N
ATOM	298	C	HIS	30	43.173	10.538	52.714	1.00	37.68	AAAA	C
ATOM	299	O	HIS	30	44.357	10.388	52.541	1.00	38.70	AAAA	O
ATOM	300	N	ILE	31	42.308	9.542	52.584	1.00	40.02	AAAA	N
ATOM	302	CA	ILE	31	42.750	8.271	51.992	1.00	39.47	AAAA	C
ATOM	303	CB	ILE	31	42.668	7.204	53.063	1.00	37.95	AAAA	C
ATOM	304	CG2	ILE	31	43.161	5.830	52.651	1.00	23.86	AAAA	C
ATOM	305	CG1	ILE	31	43.481	7.555	54.335	1.00	41.66	AAAA	C
ATOM	306	CD1	ILE	31	43.170	6.575	55.473	1.00	28.22	AAAA	C
ATOM	307	C	ILE	31	41.884	8.044	50.755	1.00	46.52	AAAA	C
ATOM	308	O	ILE	31	40.753	7.589	50.927	1.00	43.56	AAAA	O
ATOM	309	N	LEU	32	42.314	8.489	49.556	1.00	49.89	AAAA	N
ATOM	311	CA	LEU	32	41.484	8.235	48.390	1.00	49.77	AAAA	C

ATOM	312	CB	LEU	32	41.127	9.515	47.603	1.00 47.49	AAAA C
ATOM	313	CG	LEU	32	42.091	10.688	47.562	1.00 45.33	AAAA C
ATOM	314	CD1	LEU	32	41.517	11.812	46.673	1.00 35.77	AAAA C
ATOM	315	CD2	LEU	32	42.371	11.229	48.969	1.00 49.19	AAAA C
ATOM	316	C	LEU	32	42.136	7.296	47.353	1.00 51.00	AAAA C
ATOM	317	O	LEU	32	43.338	7.370	47.186	1.00 41.36	AAAA O
ATOM	318	N	LEU	33	41.270	6.722	46.497	1.00 50.74	AAAA N
ATOM	320	CA	LEU	33	41.602	6.175	45.197	1.00 49.92	AAAA C
ATOM	321	CB	LEU	33	42.091	7.262	44.182	1.00 34.83	AAAA C
ATOM	322	CG	LEU	33	41.233	8.537	44.164	1.00 33.92	AAAA C
ATOM	323	CD1	LEU	33	41.892	9.587	43.298	1.00 37.49	AAAA C
ATOM	324	CD2	LEU	33	39.823	8.313	43.644	1.00 33.01	AAAA C
ATOM	325	C	LEU	33	42.618	5.073	45.287	1.00 48.35	AAAA C
ATOM	326	O	LEU	33	43.580	5.077	44.538	1.00 54.14	AAAA O
ATOM	327	N	ILE	34	42.543	4.212	46.254	1.00 47.61	AAAA N
ATOM	329	CA	ILE	34	43.523	3.184	46.540	1.00 51.70	AAAA C
ATOM	330	CB	ILE	34	44.101	3.346	47.963	1.00 57.98	AAAA C
ATOM	331	CG2	ILE	34	44.538	2.043	48.600	1.00 48.98	AAAA C
ATOM	332	CG1	ILE	34	45.267	4.371	47.967	1.00 46.70	AAAA C
ATOM	333	CD1	ILE	34	45.561	4.704	49.439	1.00 66.47	AAAA C
ATOM	334	C	ILE	34	42.829	1.844	46.408	1.00 59.85	AAAA C
ATOM	335	O	ILE	34	41.726	1.531	46.856	1.00 60.11	AAAA O
ATOM	336	N	SER	35	43.622	0.833	46.013	1.00 67.79	AAAA N
ATOM	338	CA	SER	35	43.048	-0.511	45.922	1.00 68.80	AAAA C
ATOM	339	CB	SER	35	42.767	-0.882	44.469	1.00 64.16	AAAA C
ATOM	340	OG	SER	35	41.731	-1.846	44.498	1.00 75.76	AAAA O
ATOM	342	C	SER	35	43.928	-1.564	46.537	1.00 70.73	AAAA C
ATOM	343	O	SER	35	44.885	-1.954	45.909	1.00 73.65	AAAA O
ATOM	344	N	LYS	36	43.687	-2.017	47.740	1.00 74.75	AAAA N
ATOM	346	CA	LYS	36	44.465	-3.014	48.421	1.00 76.09	AAAA C
ATOM	347	CB	LYS	36	44.046	-3.131	49.885	1.00 81.20	AAAA C
ATOM	348	CG	LYS	36	45.147	-3.654	50.779	1.00 78.87	AAAA C
ATOM	349	CD	LYS	36	44.693	-4.575	51.887	1.00 81.39	AAAA C
ATOM	350	CE	LYS	36	44.899	-6.025	51.492	1.00 89.38	AAAA C
ATOM	351	NZ	LYS	36	44.371	-6.989	52.506	1.00 91.63	AAAA N
ATOM	355	C	LYS	36	44.252	-4.362	47.753	1.00 81.41	AAAA C
ATOM	356	O	LYS	36	43.145	-4.772	47.451	1.00 78.20	AAAA O
ATOM	357	N	ALA	37	45.371	-5.080	47.615	1.00 89.27	AAAA N
ATOM	359	CA	ALA	37	45.361	-6.396	46.986	1.00 90.10	AAAA C
ATOM	360	CB	ALA	37	46.700	-6.655	46.327	1.00 95.49	AAAA C
ATOM	361	C	ALA	37	45.011	-7.473	47.995	1.00 92.36	AAAA C
ATOM	362	O	ALA	37	45.668	-7.627	49.012	1.00 92.35	AAAA O
ATOM	363	N	SER	38	44.031	-8.301	47.622	1.00 94.31	AAAA N
ATOM	365	CA	SER	38	43.528	-9.352	48.484	1.00 95.70	AAAA C
ATOM	366	CB	SER	38	42.405	-10.164	47.858	1.00 97.44	AAAA C
ATOM	367	OG	SER	38	42.061	-11.176	48.814	1.00103.48	AAAA O
ATOM	369	C	SER	38	44.702	-10.263	48.821	1.00 96.87	AAAA C
ATOM	370	O	SER	38	44.761	-10.778	49.924	1.00 98.06	AAAA O
ATOM	371	N	ASP	39	45.584	-10.415	47.852	1.00 97.99	AAAA N
ATOM	373	CA	ASP	39	46.821	-11.148	47.980	1.00 99.19	AAAA C
ATOM	374	CB	ASP	39	47.579	-11.050	46.652	1.00102.13	AAAA C
ATOM	375	CG	ASP	39	47.696	-12.387	45.943	0.01101.22	AAAA C
ATOM	376	OD1	ASP	39	46.644	-12.978	45.623	0.01101.42	AAAA O
ATOM	377	OD2	ASP	39	48.833	-12.848	45.718	0.01101.41	AAAA O
ATOM	378	C	ASP	39	47.660	-10.564	49.105	1.00 99.40	AAAA C
ATOM	379	O	ASP	39	47.692	-11.056	50.224	1.00 99.15	AAAA O
ATOM	380	N	TYR	40	48.354	-9.479	48.818	1.00100.96	AAAA N
ATOM	382	CA	TYR	40	49.120	-8.706	49.802	1.00101.16	AAAA C
ATOM	383	CB	TYR	40	49.511	-7.393	49.130	1.00103.67	AAAA C
ATOM	384	CG	TYR	40	50.159	-6.281	49.887	1.00107.81	AAAA C
ATOM	385	CD1	TYR	40	50.931	-5.325	49.228	1.00109.56	AAAA C
ATOM	386	CE1	TYR	40	51.540	-4.280	49.910	1.00109.67	AAAA C
ATOM	387	CD2	TYR	40	50.044	-6.115	51.254	1.00109.28	AAAA C
ATOM	388	CE2	TYR	40	50.618	-5.102	51.976	1.00109.83	AAAA C
ATOM	399	CZ	TYR	40	51.372	-4.181	51.276	1.00110.16	AAAA C
ATOM	390	OH	TYR	40	51.999	-3.127	51.893	1.00109.84	AAAA O
ATOM	392	C	TYR	40	48.343	-8.529	51.100	1.00 99.10	AAAA C
ATOM	393	O	TYR	40	47.168	-8.182	51.183	1.00 99.05	AAAA O
ATOM	394	N	LYS	41	49.041	-8.653	52.218	1.00 98.62	AAAA N
ATOM	396	CA	LYS	41	48.443	-9.549	53.546	1.00100.30	AAAA C
ATOM	397	CB	LYS	41	49.385	-9.160	54.599	1.00104.42	AAAA C
ATOM	398	CG	LYS	41	49.218	-10.649	54.814	0.01101.06	AAAA C
ATOM	399	CD	LYS	41	47.776	-11.107	54.919	0.01100.66	AAAA C
ATOM	400	CE	LYS	41	47.205	-10.880	56.308	0.01 99.86	AAAA C
ATOM	401	NZ	LYS	41	47.882	-11.728	57.328	0.01 99.62	AAAA N
ATOM	405	C	LYS	41	48.035	-7.136	53.947	1.00 98.99	AAAA C
ATOM	406	O	LYS	41	47.615	-6.371	53.057	1.00103.33	AAAA O
ATOM	407	N	SER	42	48.198	-6.754	55.221	1.00 91.75	AAAA N
ATOM	409	CA	SER	42	47.825	-5.412	55.604	1.00 85.06	AAAA C
ATOM	410	CB	SER	42	46.385	-5.520	56.147	1.00 95.33	AAAA C
ATOM	411	OG	SER	42	46.547	-6.140	57.426	1.00104.63	AAAA O
ATOM	413	C	SER	42	48.628	-4.715	56.687	1.00 80.78	AAAA C
ATOM	414	O	SER	42	49.326	-5.259	57.538	1.00 81.03	AAAA O
ATOM	415	N	TYR	43	48.495	-3.395	56.673	1.00 73.03	AAAA N
ATOM	417	CA	TYR	43	49.069	-2.488	57.635	1.00 67.05	AAAA C

ATOM	418	CB	TYR	43	49.026	-1.119	56.965	1.00	65.37	AAAA C
ATOM	419	CG	TYR	43	49.953	-1.021	55.707	1.00	63.92	AAAA C
ATOM	420	CD1	TYR	43	50.931	-1.935	55.406	1.00	63.87	AAAA C
ATOM	421	CE1	TYR	43	51.698	-1.781	54.274	1.00	66.09	AAAA C
ATOM	422	CD2	TYR	43	49.779	0.090	54.870	1.00	63.30	AAAA C
ATOM	423	CE2	TYR	43	50.536	0.214	53.728	1.00	67.62	AAAA C
ATOM	424	CZ	TYR	43	51.508	-0.712	53.432	1.00	66.94	AAAA C
ATOM	425	OH	TYR	43	52.262	-0.563	52.305	1.00	69.23	AAAA O
ATOM	427	C	TYR	43	48.248	-2.381	58.925	1.00	64.88	AAAA C
ATOM	428	O	TYR	43	47.088	-2.851	59.030	1.00	62.90	AAAA O
ATOM	429	N	ARG	44	48.782	-1.567	59.825	1.00	57.88	AAAA N
ATOM	431	CA	ARG	44	48.019	-1.285	61.039	1.00	56.45	AAAA C
ATOM	432	CB	ARG	44	47.842	-2.611	61.780	1.00	46.51	AAAA C
ATOM	433	CG	ARG	44	47.915	-2.375	63.244	1.00	54.66	AAAA C
ATOM	434	CD	ARG	44	46.885	-3.327	63.986	1.00	58.54	AAAA C
ATOM	435	NE	ARG	44	47.090	-2.927	65.403	1.00	68.56	AAAA N
ATOM	437	CZ	ARG	44	46.464	-3.536	66.399	1.00	64.82	AAAA C
ATOM	438	NH1	ARG	44	45.644	-4.529	66.132	1.00	61.63	AAAA N
ATOM	441	NH2	ARG	44	46.674	-3.139	67.628	1.00	66.03	AAAA N
ATOM	444	C	ARG	44	48.911	-0.285	61.845	1.00	55.59	AAAA C
ATOM	445	O	ARG	44	49.916	-0.552	62.320	1.00	58.43	AAAA O
ATOM	446	N	PHE	45	48.276	0.866	62.139	1.00	51.13	AAAA N
ATOM	448	CA	PHE	45	48.865	1.944	62.863	1.00	45.94	AAAA C
ATOM	449	CB	PHE	45	48.774	3.249	61.978	1.00	35.89	AAAA C
ATOM	450	CG	PHE	45	49.106	2.937	60.554	1.00	30.29	AAAA C
ATOM	451	CD1	PHE	45	50.373	3.051	59.998	1.00	45.72	AAAA C
ATOM	452	CD2	PHE	45	48.127	2.428	59.728	1.00	35.95	AAAA C
ATOM	453	CE1	PHE	45	50.653	2.715	58.672	1.00	47.76	AAAA C
ATOM	454	CE2	PHE	45	48.358	2.096	58.406	1.00	39.92	AAAA C
ATOM	455	CZ	PHE	45	49.610	2.244	57.967	1.00	46.44	AAAA C
ATOM	456	C	PHE	45	48.191	2.123	64.203	1.00	41.65	AAAA C
ATOM	457	O	PHE	45	47.708	3.223	64.475	1.00	40.99	AAAA O
ATOM	458	N	PRO	46	48.494	1.338	65.212	1.00	43.20	AAAA N
ATOM	459	CD	PRO	46	49.300	0.097	65.132	1.00	47.74	AAAA C
ATOM	460	CA	PRO	46	48.032	1.530	66.560	1.00	43.34	AAAA C
ATOM	461	CB	PRO	46	48.514	0.319	67.380	1.00	44.92	AAAA C
ATOM	462	CG	PRO	46	49.404	-0.464	66.514	1.00	45.48	AAAA C
ATOM	463	C	PRO	46	48.558	2.768	67.233	1.00	41.30	AAAA C
ATOM	464	O	PRO	46	48.329	2.830	68.443	1.00	44.57	AAAA O
ATOM	465	N	LYS	47	49.450	3.553	66.676	1.00	39.33	AAAA N
ATOM	467	CA	LYS	47	49.991	4.679	67.362	1.00	38.10	AAAA C
ATOM	468	CB	LYS	47	51.378	4.981	66.852	1.00	48.07	AAAA C
ATOM	469	CG	LYS	47	52.032	3.995	65.902	1.00	67.95	AAAA C
ATOM	470	CD	LYS	47	53.563	3.976	65.891	1.00	61.33	AAAA C
ATOM	471	CE	LYS	47	54.115	4.648	67.147	1.00	72.19	AAAA C
ATOM	472	NZ	LYS	47	54.024	6.132	66.874	1.00	79.29	AAAA N
ATOM	476	C	LYS	47	49.014	5.848	67.195	1.00	39.76	AAAA C
ATOM	477	O	LYS	47	49.189	6.827	67.952	1.00	35.45	AAAA O
ATOM	478	N	LEU	48	48.300	5.886	66.053	1.00	36.45	AAAA N
ATOM	480	CA	LEU	48	47.370	7.004	65.800	1.00	40.40	AAAA C
ATOM	481	CB	LEU	48	46.823	6.919	64.389	1.00	28.59	AAAA C
ATOM	482	CG	LEU	48	45.947	7.967	63.787	1.00	31.04	AAAA C
ATOM	483	CD1	LEU	48	46.637	9.310	63.878	1.00	36.86	AAAA C
ATOM	484	CD2	LEU	48	45.591	7.738	62.294	1.00	34.49	AAAA C
ATOM	485	C	LEU	48	46.186	7.022	66.807	1.00	42.21	AAAA C
ATOM	486	O	LEU	48	45.271	6.187	66.863	1.00	36.48	AAAA O
ATOM	487	N	THR	49	46.138	8.041	67.673	1.00	38.95	AAAA N
ATOM	489	CA	THR	49	45.045	8.151	68.574	1.00	37.06	AAAA C
ATOM	490	CB	THR	49	45.548	8.207	70.034	1.00	48.69	AAAA C
ATOM	491	OG1	THR	49	46.396	9.340	70.225	1.00	35.90	AAAA O
ATOM	493	CG2	THR	49	46.230	6.957	70.529	1.00	31.99	AAAA C
ATOM	494	C	THR	49	44.230	9.425	68.321	1.00	39.48	AAAA C
ATOM	495	O	THR	49	43.111	9.451	68.837	1.00	34.49	AAAA O
ATOM	496	N	VAL	50	44.735	10.415	67.605	1.00	37.32	AAAA N
ATOM	498	CA	VAL	50	43.995	11.664	67.418	1.00	38.72	AAAA C
ATOM	499	CB	VAL	50	44.293	12.708	68.503	1.00	37.24	AAAA C
ATOM	500	CG1	VAL	50	43.630	14.066	68.208	1.00	29.96	AAAA C
ATOM	501	CG2	VAL	50	43.884	12.311	69.913	1.00	32.52	AAAA C
ATOM	502	C	VAL	50	44.271	12.305	66.048	1.00	37.03	AAAA C
ATOM	503	O	VAL	50	45.195	11.863	65.431	1.00	37.96	AAAA O
ATOM	504	N	ILE	51	43.319	12.939	65.415	1.00	37.49	AAAA N
ATOM	506	CA	ILE	51	43.301	13.575	64.133	1.00	32.48	AAAA C
ATOM	507	CB	ILE	51	42.346	12.864	63.152	1.00	34.51	AAAA C
ATOM	508	CG2	ILE	51	41.995	13.802	61.978	1.00	32.31	AAAA C
ATOM	509	CG1	ILE	51	43.026	11.611	62.671	1.00	30.78	AAAA C
ATOM	510	CD1	ILE	51	42.358	10.559	61.815	1.00	19.69	AAAA C
ATOM	511	C	ILE	51	42.659	14.939	64.431	1.00	34.14	AAAA C
ATOM	512	O	ILE	51	41.546	14.830	64.923	1.00	29.08	AAAA O
ATOM	513	N	THR	52	43.342	16.058	64.238	1.00	33.93	AAAA N
ATOM	515	CA	THR	52	42.806	17.305	64.719	1.00	33.83	AAAA C
ATOM	516	CB	THR	52	43.961	18.338	64.939	1.00	35.39	AAAA C
ATOM	517	OG1	THR	52	44.726	18.567	63.781	1.00	41.28	AAAA O
ATOM	519	CG2	THR	52	44.775	17.926	66.134	1.00	22.01	AAAA C
ATOM	520	C	THR	52	41.741	17.951	63.863	1.00	39.02	AAAA C
ATOM	521	O	THR	52	41.200	19.030	64.243	1.00	38.88	AAAA O

ATOM	522	N	GLU	53	41.524	17.477	62.633	1.00	36.93	AAAA	N
ATOM	524	CA	GLU	53	40.434	17.053	61.785	1.00	38.38	AAAA	C
ATOM	525	CB	GLU	53	41.064	18.512	60.483	1.00	29.76	AAAA	C
ATOM	526	CG	GLU	53	42.061	19.552	60.834	1.00	30.48	AAAA	C
ATOM	527	CD	GLU	53	42.517	20.396	59.697	1.00	40.82	AAAA	C
ATOM	528	OE1	GLU	53	42.638	19.908	58.556	1.00	57.56	AAAA	O
ATOM	529	OE2	GLU	53	42.799	21.559	59.931	1.00	35.74	AAAA	O
ATOM	530	C	GLU	53	39.506	16.799	61.388	1.00	39.19	AAAA	C
ATOM	531	O	GLU	53	38.922	16.311	62.386	1.00	38.95	AAAA	O
ATOM	532	N	TYR	54	39.639	16.353	60.102	1.00	30.60	AAAA	N
ATOM	534	CA	TYR	54	38.666	15.342	59.713	1.00	35.96	AAAA	C
ATOM	535	CB	TYR	54	37.654	15.802	58.636	1.00	30.71	AAAA	C
ATOM	536	CG	TYR	54	38.247	16.476	57.388	1.00	21.18	AAAA	C
ATOM	537	CD1	TYR	54	38.487	15.733	56.305	1.00	20.22	AAAA	C
ATOM	538	CE1	TYR	54	38.980	16.243	55.086	1.00	21.04	AAAA	C
ATOM	539	CD2	TYR	54	38.577	17.844	57.307	1.00	23.97	AAAA	C
ATOM	540	CE2	TYR	54	39.049	18.384	56.124	1.00	24.69	AAAA	C
ATOM	541	CZ	TYR	54	39.263	17.569	55.032	1.00	26.72	AAAA	C
ATOM	542	OH	TYR	54	39.763	18.047	53.847	1.00	37.55	AAAA	O
ATOM	544	C	TYR	54	39.405	14.115	59.142	1.00	33.87	AAAA	C
ATOM	545	O	TYR	54	40.513	14.360	58.678	1.00	30.40	AAAA	O
ATOM	546	N	LEU	55	38.683	13.021	59.004	1.00	23.24	AAAA	N
ATOM	548	CA	LEU	55	39.111	11.812	58.454	1.00	30.08	AAAA	C
ATOM	549	CB	LEU	55	39.011	10.663	59.510	1.00	14.78	AAAA	C
ATOM	550	CG	LEU	55	39.349	9.314	58.818	1.00	26.98	AAAA	C
ATOM	551	CD1	LEU	55	40.668	9.477	58.040	1.00	26.66	AAAA	C
ATOM	552	CD2	LEU	55	39.496	8.093	59.705	1.00	14.45	AAAA	C
ATOM	553	C	LEU	55	38.201	11.548	57.238	1.00	37.43	AAAA	C
ATOM	554	O	LEU	55	36.995	11.632	57.427	1.00	39.55	AAAA	O
ATOM	555	N	LEU	56	38.700	11.348	56.035	1.00	41.83	AAAA	N
ATOM	557	CA	LEU	56	37.955	11.201	54.794	1.00	36.98	AAAA	C
ATOM	558	CB	LEU	56	37.998	12.446	53.949	1.00	33.29	AAAA	C
ATOM	559	CG	LEU	56	37.984	12.514	52.416	1.00	30.35	AAAA	C
ATOM	560	CD1	LEU	56	37.076	11.460	51.821	1.00	47.95	AAAA	C
ATOM	561	CD2	LEU	56	37.286	13.807	51.985	1.00	33.47	AAAA	C
ATOM	562	C	LEU	56	38.595	10.047	54.008	1.00	39.75	AAAA	C
ATOM	563	O	LEU	56	39.714	10.205	53.547	1.00	44.38	AAAA	O
ATOM	564	N	LEU	57	37.846	9.008	53.800	1.00	36.68	AAAA	N
ATOM	566	CA	LEU	57	38.133	7.832	53.034	1.00	41.53	AAAA	C
ATOM	567	CB	LEU	57	37.944	6.588	53.916	1.00	37.00	AAAA	C
ATOM	568	CG	LEU	57	39.064	6.534	55.026	1.00	36.13	AAAA	C
ATOM	569	CD1	LEU	57	38.513	6.890	56.417	1.00	33.26	AAAA	C
ATOM	570	CD2	LEU	57	39.630	5.162	55.039	1.00	24.11	AAAA	C
ATOM	571	C	LEU	57	37.203	7.825	51.838	1.00	46.03	AAAA	C
ATOM	572	O	LEU	57	35.985	7.993	51.969	1.00	44.78	AAAA	O
ATOM	573	N	PHE	58	37.792	7.898	50.642	1.00	47.07	AAAA	N
ATOM	575	CA	PHE	58	36.895	8.002	49.467	1.00	48.75	AAAA	C
ATOM	576	CB	PHE	58	36.704	9.448	49.102	1.00	46.67	AAAA	C
ATOM	577	CG	PHE	58	36.447	9.815	47.692	1.00	54.66	AAAA	C
ATOM	578	CD1	PHE	58	37.413	9.706	46.697	1.00	55.19	AAAA	C
ATOM	579	CD2	PHE	58	35.200	10.301	47.326	1.00	53.86	AAAA	C
ATOM	580	CE1	PHE	58	37.124	10.063	45.396	1.00	50.36	AAAA	C
ATOM	581	CE2	PHE	58	34.885	10.655	46.011	1.00	41.84	AAAA	C
ATOM	582	CZ	PHE	58	35.877	10.521	45.037	1.00	46.50	AAAA	C
ATOM	583	C	PHE	58	37.351	7.052	48.379	1.00	49.71	AAAA	C
ATOM	584	O	PHE	58	38.487	7.073	47.934	1.00	52.16	AAAA	O
ATOM	585	N	ARG	59	36.471	6.118	47.944	1.00	44.26	AAAA	N
ATOM	587	CA	ARG	59	36.793	5.281	46.815	1.00	40.80	AAAA	C
ATOM	588	CB	ARG	59	36.911	5.993	45.427	1.00	23.79	AAAA	C
ATOM	589	CG	ARG	59	35.869	7.020	45.121	1.00	46.53	AAAA	C
ATOM	590	CD	ARG	59	35.921	7.562	43.706	1.00	37.64	AAAA	C
ATOM	591	NE	ARG	59	35.822	6.422	42.806	1.00	49.23	AAAA	N
ATOM	593	CZ	ARG	59	34.950	5.832	42.036	1.00	41.36	AAAA	C
ATOM	594	NH1	ARG	59	33.702	6.277	41.931	1.00	47.00	AAAA	N
ATOM	597	NH2	ARG	59	35.237	4.729	41.327	1.00	42.58	AAAA	N
ATOM	600	C	ARG	59	38.037	4.494	47.049	1.00	42.25	AAAA	C
ATOM	601	O	ARG	59	38.981	4.513	46.232	1.00	44.11	AAAA	O
ATOM	602	N	VAL	60	38.061	3.625	48.023	1.00	40.84	AAAA	N
ATOM	604	CA	VAL	60	39.101	2.743	48.341	1.00	39.14	AAAA	C
ATOM	605	CB	VAL	60	39.604	3.066	49.751	1.00	40.12	AAAA	C
ATOM	606	CG1	VAL	60	40.407	1.972	50.296	1.00	35.05	AAAA	C
ATOM	607	CG2	VAL	60	40.425	4.352	49.893	1.00	28.86	AAAA	C
ATOM	608	C	VAL	60	38.539	1.337	48.368	1.00	43.56	AAAA	C
ATOM	609	O	VAL	60	37.535	1.224	49.072	1.00	47.66	AAAA	O
ATOM	610	N	ALA	61	39.094	0.371	47.659	1.00	41.92	AAAA	N
ATOM	612	CA	ALA	61	38.617	-0.992	47.749	1.00	42.05	AAAA	C
ATOM	613	CB	ALA	61	38.302	-1.483	46.364	1.00	52.40	AAAA	C
ATOM	614	C	ALA	61	39.613	-1.934	48.386	1.00	43.08	AAAA	C
ATOM	615	O	ALA	61	40.757	-1.602	48.670	1.00	50.59	AAAA	O
ATOM	616	N	GLY	62	39.200	-3.105	48.849	1.00	45.71	AAAA	N
ATOM	618	CA	GLY	62	40.136	-4.079	49.385	1.00	45.39	AAAA	C
ATOM	619	C	GLY	62	40.262	-3.902	50.872	1.00	48.04	AAAA	C
ATOM	620	O	GLY	62	40.587	-4.835	51.604	1.00	52.34	AAAA	O
ATOM	621	N	LEU	63	39.985	-2.734	51.383	1.00	46.90	AAAA	N
ATOM	623	CA	LEU	63	40.003	-2.443	52.805	1.00	49.11	AAAA	C

ATOM	624	CB	LEU	63	40.274	-0.953	53.027	1.00	41.41	AAAA	C
ATOM	625	CG	LEU	63	40.265	-0.423	54.443	1.00	53.41	AAAA	C
ATOM	626	CD1	LEU	63	41.172	-1.164	55.416	1.00	48.27	AAAA	C
ATOM	627	CD2	LEU	63	40.637	1.047	54.246	1.00	50.51	AAAA	C
ATOM	628	C	LEU	63	38.643	-2.881	53.323	1.00	54.20	AAAA	C
ATOM	629	O	LEU	63	37.587	-2.430	52.837	1.00	57.73	AAAA	O
ATOM	630	H	GLU	64	38.658	-3.862	54.190	1.00	53.97	AAAA	H
ATOM	632	CA	GLU	64	37.462	-4.448	54.749	1.00	56.96	AAAA	C
ATOM	633	CB	GLU	64	37.689	-5.956	54.734	1.00	65.33	AAAA	C
ATOM	634	CG	GLU	64	37.832	-6.484	53.293	1.00	75.14	AAAA	C
ATOM	635	CD	GLU	64	37.104	-7.940	53.128	1.00	78.10	AAAA	C
ATOM	636	OE1	GLU	64	37.424	-8.699	54.132	1.00	63.93	AAAA	O
ATOM	637	OE2	GLU	64	37.036	-8.320	51.978	1.00	88.77	AAAA	O
ATOM	638	C	GLU	64	37.096	-4.007	56.163	1.00	57.12	AAAA	C
ATOM	639	O	GLU	64	35.986	-4.332	56.600	1.00	59.82	AAAA	O
ATOM	640	H	SER	65	37.766	-3.042	56.761	1.00	50.64	AAAA	H
ATOM	642	CA	SER	65	37.539	-2.523	58.060	1.00	47.19	AAAA	C
ATOM	643	CB	SER	65	37.743	-3.596	59.139	1.00	49.24	AAAA	C
ATOM	644	OG	SER	65	37.501	-2.971	60.429	1.00	50.90	AAAA	O
ATOM	646	C	SER	65	38.516	-1.405	58.432	1.00	48.35	AAAA	C
ATOM	647	O	SER	65	39.716	-1.692	58.374	1.00	52.75	AAAA	O
ATOM	648	H	LEU	66	38.054	-0.289	58.984	1.00	41.03	AAAA	H
ATOM	650	CA	LEU	66	38.956	0.758	59.405	1.00	41.94	AAAA	C
ATOM	651	CB	LEU	66	38.247	2.083	59.498	1.00	25.25	AAAA	C
ATOM	652	CG	LEU	66	37.283	2.476	58.402	1.00	34.49	AAAA	C
ATOM	653	CD1	LEU	66	36.974	3.951	58.512	1.00	30.81	AAAA	C
ATOM	654	CD2	LEU	66	37.767	2.200	56.994	1.00	34.34	AAAA	C
ATOM	655	C	LEU	66	39.646	0.462	60.734	1.00	45.39	AAAA	C
ATOM	656	O	LEU	66	40.762	0.947	60.927	1.00	41.05	AAAA	O
ATOM	657	H	GLY	67	39.000	-0.346	61.583	1.00	45.21	AAAA	H
ATOM	659	CA	GLY	67	39.773	-0.672	62.799	1.00	48.14	AAAA	C
ATOM	660	C	GLY	67	40.998	-1.508	62.445	1.00	44.51	AAAA	C
ATOM	661	O	GLY	67	41.855	-1.724	63.287	1.00	45.42	AAAA	O
ATOM	662	H	ASP	68	41.013	-2.189	61.309	1.00	47.60	AAAA	H
ATOM	664	CA	ASP	68	42.194	-2.834	60.738	1.00	50.99	AAAA	C
ATOM	665	CB	ASP	68	42.012	-3.417	59.361	1.00	39.43	AAAA	C
ATOM	666	CG	ASP	68	41.205	-4.678	59.311	1.00	45.82	AAAA	C
ATOM	667	OD1	ASP	68	40.912	-5.341	60.320	1.00	44.69	AAAA	O
ATOM	668	OD2	ASP	68	40.819	-5.065	58.187	1.00	47.23	AAAA	O
ATOM	669	C	ASP	68	43.363	-1.837	60.596	1.00	45.89	AAAA	C
ATOM	670	O	ASP	68	44.436	-2.269	60.903	1.00	44.84	AAAA	O
ATOM	671	H	LEU	69	43.145	-0.609	60.247	1.00	42.49	AAAA	H
ATOM	673	CA	LEU	69	44.175	0.352	60.048	1.00	45.80	AAAA	C
ATOM	674	CB	LEU	69	43.920	1.393	58.945	1.00	45.25	AAAA	C
ATOM	675	CG	LEU	69	43.902	0.882	57.494	1.00	54.25	AAAA	C
ATOM	676	CD1	LEU	69	43.541	2.037	56.565	1.00	47.26	AAAA	C
ATOM	677	CD2	LEU	69	45.211	0.200	57.113	1.00	50.76	AAAA	C
ATOM	678	C	LEU	69	44.347	1.107	61.350	1.00	49.50	AAAA	C
ATOM	679	O	LEU	69	45.470	1.210	61.851	1.00	54.51	AAAA	O
ATOM	680	H	PHE	70	43.296	1.737	61.869	1.00	44.60	AAAA	H
ATOM	682	CA	PHE	70	43.423	2.564	63.046	1.00	39.67	AAAA	C
ATOM	683	CB	PHE	70	42.987	3.973	62.700	1.00	26.08	AAAA	C
ATOM	684	CG	PHE	70	43.465	4.501	61.390	1.00	45.32	AAAA	C
ATOM	685	CD1	PHE	70	42.532	4.748	60.384	1.00	47.41	AAAA	C
ATOM	686	CD2	PHE	70	44.815	4.767	61.130	1.00	48.77	AAAA	C
ATOM	687	CE1	PHE	70	42.945	5.263	59.159	1.00	56.16	AAAA	C
ATOM	688	CE2	PHE	70	45.229	5.256	59.895	1.00	47.24	AAAA	C
ATOM	689	CZ	PHE	70	44.293	5.506	58.896	1.00	49.54	AAAA	C
ATOM	690	C	PHE	70	42.655	1.999	64.219	1.00	40.09	AAAA	C
ATOM	691	O	PHE	70	41.874	2.734	64.838	1.00	35.74	AAAA	O
ATOM	692	H	PRO	71	43.053	0.852	64.768	1.00	39.19	AAAA	H
ATOM	693	CD	PRO	71	44.269	0.058	64.411	1.00	39.94	AAAA	C
ATOM	694	CA	PRO	71	42.444	0.237	65.899	1.00	35.30	AAAA	C
ATOM	695	CB	PRO	71	43.308	-0.983	66.246	1.00	38.03	AAAA	C
ATOM	696	CG	PRO	71	44.669	-0.564	65.717	1.00	38.36	AAAA	C
ATOM	697	C	PRO	71	42.453	1.089	67.126	1.00	33.72	AAAA	C
ATOM	698	O	PRO	71	42.005	0.630	68.159	1.00	39.32	AAAA	O
ATOM	699	H	ASN	72	43.058	2.220	67.231	1.00	36.55	AAAA	H
ATOM	701	CA	ASN	72	43.204	3.032	68.401	1.00	32.60	AAAA	C
ATOM	702	CB	ASN	72	44.637	2.916	68.962	1.00	36.89	AAAA	C
ATOM	703	CG	ASN	72	44.735	1.638	69.761	1.00	47.03	AAAA	C
ATOM	704	OD1	ASN	72	44.644	1.619	70.979	1.00	64.42	AAAA	O
ATOM	705	ND2	ASN	72	44.880	0.475	69.169	1.00	63.17	AAAA	H
ATOM	708	C	ASN	72	42.875	4.477	68.135	1.00	30.11	AAAA	C
ATOM	709	O	ASN	72	43.099	5.201	69.104	1.00	36.53	AAAA	O
ATOM	710	H	LEU	73	42.309	4.809	66.978	1.00	27.62	AAAA	H
ATOM	712	CA	LEU	73	41.940	6.207	66.730	1.00	34.07	AAAA	C
ATOM	713	CB	LEU	73	41.476	6.373	65.292	1.00	28.37	AAAA	C
ATOM	714	CG	LEU	73	40.819	7.713	64.882	1.00	29.33	AAAA	C
ATOM	715	CD1	LEU	73	41.918	8.721	64.963	1.00	31.86	AAAA	C
ATOM	716	CD2	LEU	73	40.202	7.518	63.478	1.00	32.07	AAAA	C
ATOM	717	C	LEU	73	40.929	6.969	67.817	1.00	32.14	AAAA	C
ATOM	718	O	LEU	73	40.073	5.737	68.081	1.00	35.02	AAAA	O
ATOM	719	H	THR	74	41.081	7.585	68.582	1.00	29.47	AAAA	H
ATOM	721	CA	THR	74	40.150	7.826	69.683	1.00	34.80	AAAA	C

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ATOM    722  CB   THR   74    41.028    7.744   70.952   1.00 46.09    AAAA C
ATOM    723  OG1  THR   74    41.729    6.485   70.880   1.00 46.30    AAAA O
ATOM    725  CG2  THR   74    40.262    7.831   72.253   1.00 39.45    AAAA C
ATOM    726  C    THR   74    39.424    9.155   69.602   1.00 35.48    AAAA C
ATOM    727  O    THR   74    38.270    9.322   70.077   1.00 35.32    AAAA O
ATOM    728  H    VAL   75    40.047   10.199   69.073   1.00 29.80    AAAA H
ATOM    730  CA   VAL   75    39.351   11.474   68.892   1.00 34.91    AAAA C
ATOM    731  CB   VAL   75    39.856   12.445   69.955   1.00 26.03    AAAA C
ATOM    732  CG1  VAL   75    39.173   13.801   69.934   1.00 24.51    AAAA C
ATOM    733  CG2  VAL   75    39.675   11.910   71.366   1.00 19.87    AAAA C
ATOM    734  C    VAL   75    39.613   12.045   67.494   1.00 37.57    AAAA C
ATOM    735  O    VAL   75    40.724   11.808   67.022   1.00 35.99    AAAA O
ATOM    736  N    ILE   76    38.600   12.555   66.796   1.00 35.91    AAAA N
ATOM    738  CA   ILE   76    38.693   13.340   65.592   1.00 31.48    AAAA C
ATOM    739  CB   ILE   76    37.831   12.769   64.492   1.00 29.60    AAAA C
ATOM    740  CG2  ILE   76    37.856   13.630   63.208   1.00 19.54    AAAA C
ATOM    741  CG1  ILE   76    38.222   11.314   64.277   1.00 28.52    AAAA C
ATOM    742  CD1  ILE   76    37.149   10.556   63.478   1.00 28.85    AAAA C
ATOM    743  C    ILE   76    38.157   14.718   66.000   1.00 33.84    AAAA C
ATOM    744  O    ILE   76    36.987   14.777   66.274   1.00 38.84    AAAA O
ATOM    745  N    ARG   77    38.906   15.733   66.230   1.00 30.32    AAAA N
ATOM    747  CA   ARG   77    38.605   16.901   67.021   1.00 30.82    AAAA C
ATOM    748  CB   ARG   77    39.961   17.475   67.461   1.00 26.62    AAAA C
ATOM    749  CG   ARG   77    39.993   18.836   68.058   1.00 52.42    AAAA C
ATOM    750  CD   ARG   77    41.290   18.957   68.908   1.00 49.10    AAAA C
ATOM    751  NE   ARG   77    41.411   17.817   69.773   1.00 39.23    AAAA N
ATOM    753  CZ   ARG   77    40.977   18.016   71.064   1.00 48.79    AAAA C
ATOM    754  NH1  ARG   77    40.440   19.104   71.610   1.00 30.34    AAAA N
ATOM    757  NH2  ARG   77    41.061   17.012   71.941   1.00 40.38    AAAA N
ATOM    760  C    ARG   77    37.643   17.733   66.225   1.00 31.75    AAAA C
ATOM    761  O    ARG   77    36.944   18.637   66.664   1.00 31.40    AAAA O
ATOM    762  N    GLY   78    37.688   17.661   64.884   1.00 32.87    AAAA N
ATOM    764  CA   GLY   78    36.982   18.409   63.950   1.00 16.23    AAAA C
ATOM    765  C    GLY   78    37.199   19.880   64.063   1.00 31.58    AAAA C
ATOM    766  O    GLY   78    36.363   20.775   63.674   1.00 34.03    AAAA O
ATOM    767  H    TRP   79    38.439   20.321   64.304   1.00 31.21    AAAA H
ATOM    769  CA   TRP   79    38.757   21.740   64.337   1.00 30.80    AAAA C
ATOM    770  CB   TRP   79    40.177   21.943   64.845   1.00 39.07    AAAA C
ATOM    771  CG   TRP   79    40.626   23.343   65.164   1.00 36.64    AAAA C
ATOM    772  CD2  TRP   79    41.691   24.001   64.433   1.00 28.52    AAAA C
ATOM    773  CE2  TRP   79    41.826   25.288   65.002   1.00 36.49    AAAA C
ATOM    774  CE3  TRP   79    42.473   23.625   63.370   1.00 37.96    AAAA C
ATOM    775  CD1  TRP   79    40.199   24.235   66.113   1.00 29.59    AAAA C
ATOM    776  NE1  TRP   79    40.917   25.413   66.054   1.00 27.67    AAAA N
ATOM    778  CZ2  TRP   79    42.770   26.213   64.543   1.00 31.83    AAAA C
ATOM    779  CZ3  TRP   79    43.389   24.548   62.876   1.00 46.14    AAAA C
ATOM    780  CH2  TRP   79    43.525   25.794   63.470   1.00 35.31    AAAA C
ATOM    781  C    TRP   79    38.606   22.418   62.986   1.00 28.75    AAAA C
ATOM    782  O    TRP   79    38.585   23.624   62.961   1.00 23.61    AAAA O
ATOM    783  H    LYS   80    38.659   21.684   61.895   1.00 31.84    AAAA N
ATOM    785  CA   LYS   80    38.305   22.153   60.573   1.00 32.78    AAAA C
ATOM    786  CB   LYS   80    39.453   22.498   59.689   1.00 41.17    AAAA C
ATOM    787  CG   LYS   80    39.838   23.911   59.470   1.00 34.68    AAAA C
ATOM    788  CD   LYS   80    41.025   24.350   60.306   1.00 44.77    AAAA C
ATOM    789  CE   LYS   80    41.276   25.811   59.898   1.00 50.41    AAAA C
ATOM    790  NZ   LYS   80    42.530   25.752   59.092   1.00 67.26    AAAA N
ATOM    791  C    LYS   80    37.585   20.960   59.917   1.00 34.52    AAAA C
ATOM    792  O    LYS   80    37.950   19.843   60.237   1.00 37.62    AAAA O
ATOM    793  H    LEU   81    36.477   21.267   59.207   1.00 31.77    AAAA H
ATOM    795  CA   LEU   81    35.742   20.157   58.600   1.00 31.02    AAAA C
ATOM    796  CB   LEU   81    34.290   20.315   59.092   1.00 31.20    AAAA C
ATOM    797  CG   LEU   81    34.115   20.319   60.632   1.00 36.97    AAAA C
ATOM    798  CD1  LEU   81    32.832   21.080   60.954   1.00 27.98    AAAA C
ATOM    799  CD2  LEU   81    34.089   18.955   61.297   1.00 28.77    AAAA C
ATOM    800  C    LEU   81    35.733   20.023   57.104   1.00 29.86    AAAA C
ATOM    801  O    LEU   81    36.082   20.947   56.368   1.00 29.34    AAAA O
ATOM    802  H    PHE   82    35.430   18.813   56.594   1.00 27.78    AAAA H
ATOM    804  CA   PHE   82    35.176   18.653   55.182   1.00 28.68    AAAA C
ATOM    805  CB   PHE   82    35.513   17.226   54.795   1.00 32.78    AAAA C
ATOM    806  CG   PHE   82    35.348   16.901   53.357   1.00 30.48    AAAA C
ATOM    807  CD1  PHE   82    36.378   17.130   52.447   1.00 32.86    AAAA C
ATOM    808  CD2  PHE   82    34.142   16.361   52.914   1.00 30.93    AAAA C
ATOM    809  CE1  PHE   82    36.217   16.769   51.104   1.00 43.27    AAAA C
ATOM    810  CE2  PHE   82    33.963   16.061   51.538   1.00 26.30    AAAA C
ATOM    811  CZ   PHE   82    35.005   16.238   50.672   1.00 37.73    AAAA C
ATOM    812  C    PHE   82    33.670   18.911   54.993   1.00 30.06    AAAA C
ATOM    813  O    PHE   82    32.830   18.045   55.278   1.00 27.36    AAAA O
ATOM    814  H    TYR   83    33.301   20.148   54.770   1.00 31.68    AAAA H
ATOM    815  CA   TYR   83    31.911   20.605   54.633   1.00 40.76    AAAA C
ATOM    816  C    TYR   83    31.043   19.977   55.726   1.00 44.00    AAAA C
ATOM    817  O    TYR   83    30.075   19.210   55.487   1.00 50.47    AAAA O
ATOM    818  CB   TYR   83    31.359   20.199   53.269   1.00 31.55    AAAA C
ATOM    819  CG   TYR   83    32.196   20.742   52.117   0.01 20.00    AAAA C
ATOM    820  CD1  TYR   83    33.254   19.982   51.609   0.01 20.00    AAAA C
ATOM    821  CD2  TYR   83    31.906   21.998   51.575   0.01 20.00    AAAA C
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ATOM	822	CE1	TYR	83	34.027	20.480	50.556	0.01	20.00	AAAA	C
ATOM	823	CE2	TYR	83	32.679	22.496	50.521	0.01	20.00	AAAA	C
ATOM	824	CZ	TYR	83	33.740	21.737	50.012	0.01	20.00	AAAA	O
ATOM	825	OH	TYR	83	34.492	22.222	48.989	0.01	20.00	AAAA	O
ATOM	826	N	ASN	84	31.043	20.461	56.924	1.00	40.91	AAAA	N
ATOM	827	CA	ASN	84	30.250	20.057	58.056	1.00	36.54	AAAA	C
ATOM	828	CB	ASN	84	28.763	20.046	57.700	1.00	47.84	AAAA	C
ATOM	829	CG	ASN	84	28.274	21.164	56.797	1.00	60.75	AAAA	C
ATOM	830	OD1	ASN	84	28.319	22.343	57.119	1.00	45.55	AAAA	O
ATOM	831	ND2	ASN	84	27.839	20.876	55.552	1.00	65.98	AAAA	N
ATOM	832	C	ASN	84	30.686	18.679	58.556	1.00	36.33	AAAA	C
ATOM	833	O	ASN	84	30.137	18.206	59.580	1.00	38.24	AAAA	O
ATOM	834	N	TYR	85	31.455	17.900	57.800	1.00	32.78	AAAA	N
ATOM	836	CA	TYR	85	31.617	16.504	58.222	1.00	35.45	AAAA	C
ATOM	837	CB	TYR	85	31.473	15.579	57.000	1.00	35.54	AAAA	C
ATOM	838	CG	TYR	85	30.078	15.733	56.453	1.00	41.35	AAAA	C
ATOM	839	CD1	TYR	85	29.868	16.291	55.199	1.00	38.22	AAAA	C
ATOM	840	CE1	TYR	85	28.611	16.445	54.704	1.00	40.83	AAAA	C
ATOM	841	CD2	TYR	85	28.954	15.371	57.200	1.00	47.42	AAAA	C
ATOM	842	CE2	TYR	85	27.661	15.533	56.705	1.00	45.91	AAAA	C
ATOM	843	CZ	TYR	85	27.497	16.072	55.445	1.00	46.06	AAAA	C
ATOM	844	OH	TYR	85	26.258	16.315	54.886	1.00	46.05	AAAA	O
ATOM	846	C	TYR	85	32.977	16.367	58.891	1.00	32.09	AAAA	C
ATOM	847	O	TYR	85	33.943	16.977	58.495	1.00	37.44	AAAA	O
ATOM	848	N	ALA	86	33.027	15.691	59.979	1.00	30.21	AAAA	N
ATOM	850	CA	ALA	86	34.257	15.325	60.670	1.00	34.10	AAAA	C
ATOM	851	CB	ALA	86	33.999	15.370	62.157	1.00	25.48	AAAA	C
ATOM	852	C	ALA	86	34.729	13.962	60.216	1.00	32.67	AAAA	C
ATOM	853	O	ALA	86	35.795	13.481	60.577	1.00	35.10	AAAA	O
ATOM	854	N	LEU	87	33.832	13.173	59.597	1.00	28.56	AAAA	N
ATOM	856	CA	LEU	87	34.188	11.805	59.323	1.00	29.26	AAAA	C
ATOM	857	CB	LEU	87	33.798	10.860	60.471	1.00	13.64	AAAA	C
ATOM	858	CG	LEU	87	33.801	9.363	60.188	1.00	25.77	AAAA	C
ATOM	859	CD1	LEU	87	35.140	8.915	59.571	1.00	27.21	AAAA	C
ATOM	860	CD2	LEU	87	33.637	8.432	61.393	1.00	23.52	AAAA	C
ATOM	861	C	LEU	87	33.530	11.429	58.001	1.00	35.60	AAAA	C
ATOM	862	O	LEU	87	32.320	11.421	58.001	1.00	38.97	AAAA	O
ATOM	863	N	VAL	88	34.174	11.300	56.875	1.00	37.86	AAAA	N
ATOM	865	CA	VAL	88	33.438	11.032	55.628	1.00	33.32	AAAA	C
ATOM	866	CB	VAL	88	33.666	12.085	54.553	1.00	22.38	AAAA	C
ATOM	867	CG1	VAL	88	32.974	11.675	53.261	1.00	19.24	AAAA	C
ATOM	868	CG2	VAL	88	33.165	13.402	55.042	1.00	13.27	AAAA	C
ATOM	869	C	VAL	88	33.898	9.684	55.114	1.00	31.79	AAAA	C
ATOM	870	O	VAL	88	35.069	9.407	55.117	1.00	33.57	AAAA	O
ATOM	871	N	ILE	89	33.078	8.728	54.822	1.00	31.08	AAAA	N
ATOM	873	CA	ILE	89	33.361	7.433	54.280	1.00	30.45	AAAA	C
ATOM	874	CB	ILE	89	32.941	6.384	55.296	1.00	30.17	AAAA	C
ATOM	875	CG2	ILE	89	32.898	4.954	54.821	1.00	37.24	AAAA	C
ATOM	876	CG1	ILE	89	33.893	6.420	56.500	1.00	24.92	AAAA	C
ATOM	877	CD1	ILE	89	33.424	5.613	57.675	1.00	23.96	AAAA	C
ATOM	878	C	ILE	89	32.509	7.206	53.027	1.00	40.64	AAAA	C
ATOM	879	O	ILE	89	31.330	6.881	53.205	1.00	38.69	AAAA	O
ATOM	880	N	PHE	90	33.082	7.464	51.845	1.00	41.45	AAAA	N
ATOM	882	CA	PHE	90	32.346	7.371	50.591	1.00	37.67	AAAA	C
ATOM	883	CB	PHE	90	32.347	8.776	50.110	1.00	32.17	AAAA	C
ATOM	884	CG	PHE	90	31.591	9.081	48.865	1.00	39.77	AAAA	C
ATOM	885	CD1	PHE	90	30.387	9.772	49.025	1.00	32.02	AAAA	C
ATOM	886	CD2	PHE	90	32.052	8.721	47.620	1.00	29.28	AAAA	C
ATOM	887	CE1	PHE	90	29.611	10.111	47.938	1.00	33.39	AAAA	C
ATOM	888	CE2	PHE	90	31.290	9.086	46.534	1.00	43.09	AAAA	C
ATOM	889	CZ	PHE	90	30.083	9.764	46.687	1.00	50.24	AAAA	C
ATOM	890	C	PHE	90	32.856	6.384	49.557	1.00	40.72	AAAA	C
ATOM	891	O	PHE	90	34.007	6.296	49.203	1.00	46.15	AAAA	O
ATOM	892	N	GLU	91	32.024	5.519	49.001	1.00	39.16	AAAA	N
ATOM	894	CA	GLU	91	32.248	4.601	47.954	1.00	42.45	AAAA	C
ATOM	895	CB	GLU	91	32.479	5.231	46.583	1.00	38.08	AAAA	C
ATOM	896	CG	GLU	91	31.136	5.865	46.250	1.00	58.86	AAAA	C
ATOM	897	CD	GLU	91	30.855	5.776	44.757	1.00	63.55	AAAA	C
ATOM	898	OE1	GLU	91	31.473	6.651	44.082	1.00	64.10	AAAA	O
ATOM	899	OE2	GLU	91	30.059	4.813	44.573	1.00	63.64	AAAA	O
ATOM	900	C	GLU	91	33.422	3.734	48.313	1.00	42.06	AAAA	C
ATOM	901	O	GLU	91	34.298	3.411	47.587	1.00	44.71	AAAA	O
ATOM	902	N	MET	92	33.352	3.209	49.482	1.00	46.52	AAAA	N
ATOM	904	CA	MET	92	34.409	2.401	50.088	1.00	42.26	AAAA	C
ATOM	905	CB	MET	92	34.299	2.659	51.584	1.00	38.37	AAAA	C
ATOM	906	CG	MET	92	35.412	2.156	52.420	1.00	59.39	AAAA	C
ATOM	907	SD	MET	92	36.802	3.306	52.401	1.00	57.67	AAAA	S
ATOM	908	CE	MET	92	36.340	4.405	51.108	1.00	38.36	AAAA	C
ATOM	909	C	MET	92	34.012	1.005	49.745	1.00	43.37	AAAA	C
ATOM	910	O	MET	92	33.335	0.298	50.523	1.00	45.58	AAAA	O
ATOM	911	N	THR	93	34.449	0.518	48.602	1.00	47.09	AAAA	N
ATOM	913	CA	THR	93	34.175	-0.900	48.273	1.00	47.32	AAAA	C
ATOM	914	CB	THR	93	34.668	-1.281	46.868	1.00	55.29	AAAA	C
ATOM	915	OG1	THR	93	34.013	-0.488	45.892	1.00	57.81	AAAA	O
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ATOM   1015   CD1  LEU   103   36.606    8.513   66.646   1.00  23.20     AAAA  C
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ATOM	1022	CB	ARG	104	35.568	7.657	73.019	1.00	38.17	AAAA	C
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ATOM	1107	NE	ARG	112	27.950	12.726	51.770	1.00	50.34	AAAA	N
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ATOM	1124	CD1	ILE	113	29.324	6.250	59.176	1.00	42.34	AAAA	C
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ATOM	1129	CA	GLU	114	27.491	7.103	51.935	1.00	38.76	AAAA	C
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ATOM	1131	CG	GLU	114	26.567	8.402	49.969	1.00	27.97	AAAA	C
ATOM	1132	CD	GLU	114	26.349	9.840	49.578	1.00	36.85	AAAA	C
ATOM	1133	OE1	GLU	114	26.763	10.662	50.414	1.00	45.57	AAAA	O

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ATOM	1135	C	GLU	114	28.039	6.072	50.944	1.00	44.17	AAAA	C
ATOM	1136	O	GLU	114	29.120	5.538	51.090	1.00	49.97	AAAA	O
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ATOM	1142	CD	LYS	115	26.537	6.355	45.982	1.00	24.74	AAAA	C
ATOM	1143	CE	LYS	115	26.751	7.804	45.622	1.00	41.86	AAAA	C
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ATOM	1161	N	ALA	117	27.989	-0.188	49.772	1.00	40.94	AAAA	N
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ATOM	1170	CB	ASP	118	29.659	-4.945	51.477	1.00	55.39	AAAA	C
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ATOM	1174	C	ASP	118	28.818	-3.586	53.353	1.00	37.29	AAAA	C
ATOM	1175	O	ASP	118	29.127	-4.536	54.026	1.00	42.89	AAAA	O
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ATOM	1178	CA	LEU	119	28.986	-1.885	55.047	1.00	40.58	AAAA	C
ATOM	1179	CB	LEU	119	29.159	-0.389	55.145	1.00	34.31	AAAA	C
ATOM	1180	CG	LEU	119	29.640	0.331	56.378	1.00	36.58	AAAA	C
ATOM	1181	CD1	LEU	119	30.950	-0.101	56.948	1.00	35.77	AAAA	C
ATOM	1182	CD2	LEU	119	29.791	1.830	56.104	1.00	29.68	AAAA	C
ATOM	1183	C	LEU	119	27.937	-2.376	56.007	1.00	43.67	AAAA	C
ATOM	1184	O	LEU	119	26.748	-2.248	55.743	1.00	45.32	AAAA	O
ATOM	1185	N	CYS	120	28.361	-2.967	57.110	1.00	43.53	AAAA	N
ATOM	1187	CA	CYS	120	27.378	-3.407	58.089	1.00	38.93	AAAA	C
ATOM	1188	C	CYS	120	27.881	-2.921	59.426	1.00	41.91	AAAA	C
ATOM	1189	O	CYS	120	28.660	-1.960	59.446	1.00	43.66	AAAA	O
ATOM	1190	CB	CYS	120	27.285	-4.907	58.100	1.00	37.59	AAAA	C
ATOM	1191	SG	CYS	120	26.568	-5.622	56.639	1.00	58.32	AAAA	S
ATOM	1192	N	TYR	121	27.328	-3.456	60.509	1.00	38.05	AAAA	N
ATOM	1194	CA	TYR	121	27.795	-3.010	61.927	1.00	39.68	AAAA	C
ATOM	1195	CB	TYR	121	29.189	-3.572	62.130	1.00	34.61	AAAA	C
ATOM	1196	CG	TYR	121	28.950	-5.032	62.519	1.00	36.50	AAAA	C
ATOM	1197	CD1	TYR	121	29.087	-6.045	61.582	1.00	33.58	AAAA	C
ATOM	1198	CE1	TYR	121	28.852	-7.350	61.980	1.00	41.21	AAAA	C
ATOM	1199	CD2	TYR	121	28.560	-5.337	63.817	1.00	36.31	AAAA	C
ATOM	1200	CE2	TYR	121	28.297	-6.630	64.201	1.00	39.48	AAAA	C
ATOM	1201	CZ	TYR	121	28.432	-7.641	63.270	1.00	46.07	AAAA	C
ATOM	1202	OH	TYR	121	28.161	-8.924	63.730	1.00	49.20	AAAA	O
ATOM	1204	C	TYR	121	27.674	-1.523	61.789	1.00	38.83	AAAA	O
ATOM	1205	O	TYR	121	28.445	-0.778	62.369	1.00	43.22	AAAA	O
ATOM	1206	N	LEU	122	26.587	-1.045	61.180	1.00	39.58	AAAA	N
ATOM	1208	CA	LEU	122	26.361	0.405	61.098	1.00	44.82	AAAA	C
ATOM	1209	CB	LEU	122	25.990	0.715	59.634	1.00	46.48	AAAA	C
ATOM	1210	CG	LEU	122	26.497	2.014	59.108	1.00	44.44	AAAA	C
ATOM	1211	CD1	LEU	122	25.778	2.448	57.859	1.00	32.19	AAAA	C
ATOM	1212	CD2	LEU	122	26.136	3.057	60.170	1.00	47.76	AAAA	C
ATOM	1213	C	LEU	122	25.212	0.910	61.935	1.00	44.85	AAAA	C
ATOM	1214	O	LEU	122	25.269	1.759	62.839	1.00	47.66	AAAA	O
ATOM	1215	N	SER	123	24.104	0.137	61.843	1.00	40.12	AAAA	N
ATOM	1217	CA	SER	123	22.949	0.435	62.703	1.00	33.88	AAAA	C
ATOM	1218	CB	SER	123	21.754	-0.330	62.239	1.00	19.26	AAAA	C
ATOM	1219	OG	SER	123	21.964	-1.762	62.402	1.00	34.35	AAAA	O
ATOM	1221	C	SER	123	23.165	0.060	64.159	1.00	37.43	AAAA	C
ATOM	1222	O	SER	123	22.326	0.280	65.025	1.00	35.33	AAAA	O
ATOM	1223	N	THR	124	24.242	-0.698	64.432	1.00	39.03	AAAA	N
ATOM	1225	CA	THR	124	24.554	-1.165	65.753	1.00	37.78	AAAA	C
ATOM	1226	CB	THR	124	25.368	-2.461	65.719	1.00	42.39	AAAA	C
ATOM	1227	OG1	THR	124	26.502	-2.020	64.924	1.00	47.70	AAAA	O
ATOM	1229	CG2	THR	124	24.677	-3.622	65.006	1.00	40.93	AAAA	C
ATOM	1230	C	THR	124	25.522	-0.206	66.445	1.00	39.29	AAAA	C
ATOM	1231	O	THR	124	25.948	-0.642	67.499	1.00	41.41	AAAA	O
ATOM	1232	N	VAL	125	25.737	1.001	65.985	1.00	37.80	AAAA	N
ATOM	1234	CA	VAL	125	26.594	1.964	66.661	1.00	41.06	AAAA	C
ATOM	1235	CB	VAL	125	27.683	2.542	65.714	1.00	39.50	AAAA	C
ATOM	1236	CG1	VAL	125	28.570	3.599	66.352	1.00	28.36	AAAA	C
ATOM	1237	CG2	VAL	125	28.693	1.565	65.110	1.00	33.07	AAAA	C

ATOM	1238	C	VAL	125	25.759	3.127	67.173	1.00	41.17	AAAA C
ATOM	1239	O	VAL	125	24.941	3.750	66.531	1.00	41.22	AAAA O
ATOM	1240	N	ASP	126	26.072	3.636	68.367	1.00	44.54	AAAA N
ATOM	1242	CA	ASP	126	25.310	4.734	68.967	1.00	37.44	AAAA C
ATOM	1243	CB	ASP	126	24.862	4.335	70.342	1.00	34.73	AAAA C
ATOM	1244	CG	ASP	126	23.879	5.303	70.993	1.00	45.53	AAAA C
ATOM	1245	OD1	ASP	126	23.699	6.520	70.685	1.00	27.71	AAAA O
ATOM	1246	OD2	ASP	126	23.220	4.865	71.964	1.00	52.32	AAAA O
ATOM	1247	C	ASP	126	26.146	5.985	68.872	1.00	40.83	AAAA C
ATOM	1248	O	ASP	126	26.740	6.400	69.888	1.00	42.78	AAAA O
ATOM	1249	N	TRP	127	26.029	6.649	67.704	1.00	35.42	AAAA N
ATOM	1251	CA	TRP	127	26.777	7.856	67.410	1.00	33.02	AAAA C
ATOM	1252	CB	TRP	127	26.568	8.296	65.930	1.00	24.89	AAAA C
ATOM	1253	CG	TRP	127	27.195	7.372	64.907	1.00	34.36	AAAA C
ATOM	1254	CD2	TRP	127	28.587	7.208	64.518	1.00	28.60	AAAA C
ATOM	1255	CE2	TRP	127	28.631	6.186	63.579	1.00	29.06	AAAA C
ATOM	1256	CE3	TRP	127	29.770	7.845	64.873	1.00	35.51	AAAA C
ATOM	1257	CD1	TRP	127	26.465	6.450	64.188	1.00	18.67	AAAA C
ATOM	1258	NE1	TRP	127	27.311	5.712	63.394	1.00	42.87	AAAA N
ATOM	1260	CZ2	TRP	127	29.792	5.783	62.954	1.00	32.53	AAAA C
ATOM	1261	CZ3	TRP	127	30.972	7.445	64.285	1.00	31.51	AAAA C
ATOM	1262	CH2	TRP	127	30.937	6.405	63.336	1.00	37.86	AAAA C
ATOM	1263	C	TRP	127	26.558	9.010	68.367	1.00	36.09	AAAA C
ATOM	1264	O	TRP	127	27.382	9.977	68.497	1.00	40.87	AAAA O
ATOM	1265	N	SER	128	25.493	8.931	69.171	1.00	31.24	AAAA N
ATOM	1267	CA	SER	128	25.201	10.041	70.081	1.00	34.04	AAAA C
ATOM	1268	CB	SER	128	23.757	10.042	70.603	1.00	36.87	AAAA C
ATOM	1269	OG	SER	128	23.433	8.917	71.424	1.00	28.96	AAAA O
ATOM	1271	C	SER	128	26.133	9.975	71.292	1.00	32.39	AAAA C
ATOM	1272	O	SER	128	26.212	10.957	72.134	1.00	30.91	AAAA O
ATOM	1273	N	LEU	129	26.662	8.792	71.549	1.00	27.18	AAAA N
ATOM	1275	CA	LEU	129	27.701	8.607	72.526	1.00	36.73	AAAA C
ATOM	1276	CB	LEU	129	27.920	7.132	72.741	1.00	32.53	AAAA C
ATOM	1277	CG	LEU	129	26.795	6.324	73.371	1.00	39.28	AAAA C
ATOM	1278	CD1	LEU	129	27.292	5.024	73.975	1.00	32.54	AAAA C
ATOM	1279	CD2	LEU	129	26.237	7.117	74.560	1.00	32.12	AAAA C
ATOM	1280	C	LEU	129	29.054	9.226	72.113	1.00	38.04	AAAA C
ATOM	1281	O	LEU	129	29.645	10.001	72.874	1.00	34.50	AAAA O
ATOM	1282	N	ILE	130	29.316	9.217	70.807	1.00	42.09	AAAA N
ATOM	1284	CA	ILE	130	30.480	9.743	70.144	1.00	41.35	AAAA C
ATOM	1285	CB	ILE	130	30.793	8.886	68.901	1.00	41.73	AAAA C
ATOM	1286	CG2	ILE	130	31.992	9.434	68.176	1.00	31.95	AAAA C
ATOM	1287	CG1	ILE	130	30.969	7.413	69.347	1.00	26.64	AAAA C
ATOM	1288	CD1	ILE	130	31.053	6.457	68.165	1.00	42.65	AAAA C
ATOM	1289	C	ILE	130	30.305	11.178	69.679	1.00	46.49	AAAA C
ATOM	1290	O	ILE	130	31.224	11.985	69.966	1.00	38.46	AAAA O
ATOM	1291	N	LEU	131	29.089	11.495	69.193	1.00	45.14	AAAA N
ATOM	1293	CA	LEU	131	28.895	12.865	68.651	1.00	41.45	AAAA C
ATOM	1294	CB	LEU	131	28.499	12.616	67.259	1.00	46.81	AAAA C
ATOM	1295	CG	LEU	131	28.923	12.805	65.878	1.00	36.79	AAAA C
ATOM	1296	CD1	LEU	131	29.128	11.405	65.324	1.00	30.15	AAAA C
ATOM	1297	CD2	LEU	131	27.625	13.581	65.334	1.00	19.92	AAAA C
ATOM	1298	C	LEU	131	27.661	13.525	69.285	1.00	39.28	AAAA C
ATOM	1299	O	LEU	131	26.599	12.867	69.311	1.00	37.75	AAAA O
ATOM	1300	N	ASP	132	27.742	14.811	69.518	1.00	33.73	AAAA N
ATOM	1302	CA	ASP	132	26.610	15.542	70.003	1.00	38.20	AAAA C
ATOM	1303	CB	ASP	132	27.017	16.944	70.381	1.00	43.17	AAAA C
ATOM	1304	CG	ASP	132	27.349	17.137	71.834	1.00	43.29	AAAA C
ATOM	1305	OD1	ASP	132	27.536	16.122	72.521	1.00	47.12	AAAA O
ATOM	1306	OD2	ASP	132	27.413	18.331	72.208	1.00	60.58	AAAA O
ATOM	1307	C	ASP	132	25.520	15.659	68.946	1.00	43.46	AAAA C
ATOM	1308	O	ASP	132	24.481	15.032	68.939	1.00	49.32	AAAA O
ATOM	1309	N	ALA	133	25.754	16.398	67.900	1.00	45.03	AAAA N
ATOM	1311	CA	ALA	133	24.947	16.776	66.773	1.00	38.62	AAAA C
ATOM	1312	CB	ALA	133	25.628	17.987	66.092	1.00	33.82	AAAA C
ATOM	1313	C	ALA	133	24.694	15.669	65.775	1.00	33.33	AAAA C
ATOM	1314	O	ALA	133	24.777	15.791	64.517	1.00	33.71	AAAA O
ATOM	1315	N	VAL	134	24.115	14.565	66.219	1.00	27.88	AAAA N
ATOM	1317	CA	VAL	134	23.813	13.440	65.377	1.00	29.90	AAAA C
ATOM	1318	CB	VAL	134	23.202	12.241	66.120	1.00	40.63	AAAA C
ATOM	1319	CG1	VAL	134	24.265	11.441	66.855	1.00	35.20	AAAA C
ATOM	1320	CG2	VAL	134	22.095	12.701	67.068	1.00	30.84	AAAA C
ATOM	1321	C	VAL	134	22.735	13.732	64.353	1.00	36.98	AAAA C
ATOM	1322	O	VAL	134	22.616	13.106	63.292	1.00	32.95	AAAA O
ATOM	1323	N	SER	135	21.920	14.777	64.626	1.00	39.65	AAAA N
ATOM	1325	CA	SER	135	20.886	15.139	63.692	1.00	43.12	AAAA C
ATOM	1326	CB	SER	135	20.093	16.277	64.305	1.00	45.19	AAAA C
ATOM	1327	OG	SER	135	20.882	17.369	64.684	1.00	39.25	AAAA O
ATOM	1329	C	SER	135	21.396	15.516	62.309	1.00	41.15	AAAA C
ATOM	1330	O	SER	135	20.815	15.642	61.359	1.00	43.81	AAAA O
ATOM	1331	N	ASN	136	22.615	15.911	62.165	1.00	41.11	AAAA N
ATOM	1333	CA	ASN	136	23.298	16.353	60.978	1.00	37.21	AAAA C
ATOM	1334	CB	ASN	136	24.324	17.372	61.399	1.00	39.66	AAAA C
ATOM	1335	CG	ASN	136	23.724	18.709	61.717	1.00	36.59	AAAA C
ATOM	1336	OD1	ASN	136	22.695	19.079	61.149	1.00	50.81	AAAA O

ATOM	1337	HD2	ASN	136	24.379	19.441	62.585	1.00 47.85	AAAA H
ATOM	1340	C	ASN	136	21.031	15.230	60.259	1.00 35.31	AAAA C
ATOM	1341	O	ASN	136	24.535	15.484	59.194	1.00 38.70	AAAA O
ATOM	1342	H	ASN	137	24.057	14.035	60.793	1.00 29.11	AAAA H
ATOM	1344	CA	ASN	137	24.721	12.959	60.126	1.00 32.98	AAAA C
ATOM	1345	CB	ASN	137	24.737	11.703	61.033	1.00 24.45	AAAA C
ATOM	1346	CG	ASN	137	25.631	11.965	62.217	1.00 26.63	AAAA C
ATOM	1347	OD1	ASN	137	26.070	13.121	62.369	1.00 30.22	AAAA O
ATOM	1348	HD2	ASN	137	25.830	10.923	63.000	1.00 18.90	AAAA H
ATOM	1351	C	ASN	137	23.959	12.749	58.817	1.00 35.89	AAAA C
ATOM	1352	O	ASN	137	22.716	12.755	58.855	1.00 38.57	AAAA O
ATOM	1353	H	TYR	138	24.592	12.251	57.785	1.00 32.86	AAAA H
ATOM	1355	CA	TYR	138	24.093	11.983	56.489	1.00 30.25	AAAA C
ATOM	1356	CB	TYR	138	24.682	12.861	55.421	1.00 27.10	AAAA C
ATOM	1357	CG	TYR	138	24.918	12.741	54.078	1.00 37.89	AAAA C
ATOM	1358	CD1	TYR	138	23.093	13.671	53.648	1.00 39.22	AAAA C
ATOM	1359	CE1	TYR	138	22.519	13.579	52.392	1.00 37.65	AAAA C
ATOM	1360	CD2	TYR	138	24.357	11.717	53.195	1.00 44.29	AAAA C
ATOM	1361	CE2	TYR	138	23.801	11.615	51.951	1.00 41.97	AAAA C
ATOM	1362	CG	TYR	138	22.868	12.562	51.564	1.00 39.42	AAAA C
ATOM	1363	OH	TYR	138	22.296	12.504	50.318	1.00 45.48	AAAA O
ATOM	1365	C	TYR	138	24.373	10.578	56.051	1.00 31.33	AAAA C
ATOM	1366	O	TYR	138	25.505	10.317	55.797	1.00 37.76	AAAA O
ATOM	1367	H	ILE	139	23.461	9.660	56.116	1.00 35.40	AAAA H
ATOM	1369	CA	ILE	139	23.637	8.249	55.935	1.00 34.04	AAAA C
ATOM	1370	CB	ILE	139	23.234	7.450	57.171	1.00 28.66	AAAA C
ATOM	1371	CG2	ILE	139	23.640	5.984	57.093	1.00 21.99	AAAA C
ATOM	1372	CG1	ILE	139	23.711	8.057	58.469	1.00 42.81	AAAA C
ATOM	1373	CD1	ILE	139	24.455	7.100	59.389	1.00 52.23	AAAA C
ATOM	1374	C	ILE	139	22.729	7.708	54.830	1.00 35.73	AAAA C
ATOM	1375	O	ILE	139	21.538	7.890	54.757	1.00 42.61	AAAA O
ATOM	1376	H	VAL	140	23.286	6.997	53.873	1.00 35.29	AAAA H
ATOM	1378	CA	VAL	140	22.533	6.481	52.755	1.00 32.39	AAAA C
ATOM	1379	CB	VAL	140	21.967	7.627	51.881	1.00 36.05	AAAA C
ATOM	1380	CG1	VAL	140	22.800	8.375	50.881	1.00 25.88	AAAA C
ATOM	1381	CG2	VAL	140	20.807	7.034	51.047	1.00 34.96	AAAA C
ATOM	1382	C	VAL	140	23.422	5.670	51.874	1.00 41.96	AAAA C
ATOM	1383	O	VAL	140	24.537	6.172	51.637	1.00 44.03	AAAA O
ATOM	1384	H	GLY	141	22.899	4.562	51.402	1.00 42.66	AAAA H
ATOM	1386	CA	GLY	141	23.381	3.805	50.278	1.00 30.94	AAAA C
ATOM	1387	C	GLY	141	24.265	2.696	50.835	1.00 38.98	AAAA C
ATOM	1388	O	GLY	141	25.132	2.003	50.176	1.00 35.87	AAAA O
ATOM	1389	H	ASN	142	23.985	2.418	52.116	1.00 38.92	AAAA H
ATOM	1391	CA	ASN	142	24.858	1.390	52.746	1.00 44.32	AAAA C
ATOM	1392	CB	ASN	142	25.257	1.774	54.187	1.00 43.12	AAAA C
ATOM	1393	CG	ASN	142	26.131	3.022	54.152	1.00 42.00	AAAA C
ATOM	1394	OD1	ASN	142	26.984	3.077	53.269	1.00 40.47	AAAA O
ATOM	1395	HD2	ASN	142	25.945	4.022	55.019	1.00 41.98	AAAA H
ATOM	1398	C	ASN	142	24.153	0.066	52.687	1.00 45.84	AAAA C
ATOM	1399	O	ASN	142	23.113	-0.015	52.055	1.00 49.65	AAAA O
ATOM	1400	H	LYS	143	24.374	-0.990	53.272	1.00 45.23	AAAA H
ATOM	1402	CA	LYS	143	24.073	-2.299	53.195	1.00 49.14	AAAA C
ATOM	1403	CB	LYS	143	25.166	-3.328	53.433	1.00 41.49	AAAA C
ATOM	1404	CG	LYS	143	24.750	-4.686	53.832	1.00 44.96	AAAA C
ATOM	1405	CD	LYS	143	25.512	-5.743	53.100	1.00 48.66	AAAA C
ATOM	1406	CE	LYS	143	25.043	-7.131	53.558	1.00 38.35	AAAA C
ATOM	1407	HZ	LYS	143	26.080	-8.093	53.040	1.00 53.83	AAAA H
ATOM	1411	C	LYS	143	22.902	-2.431	54.169	1.00 52.85	AAAA C
ATOM	1412	O	LYS	143	22.960	-2.099	55.360	1.00 55.21	AAAA O
ATOM	1413	H	PRO	144	21.806	-3.047	53.731	1.00 52.39	AAAA H
ATOM	1414	CD	PRO	144	21.617	-3.469	52.315	1.00 52.58	AAAA C
ATOM	1415	CA	PRO	144	20.559	-3.118	54.489	1.00 48.30	AAAA C
ATOM	1416	CB	PRO	144	19.549	-3.602	53.455	1.00 51.41	AAAA C
ATOM	1417	CG	PRO	144	20.134	-3.299	52.099	1.00 50.41	AAAA C
ATOM	1418	C	PRO	144	20.621	-4.050	55.659	1.00 44.65	AAAA C
ATOM	1419	O	PRO	144	20.904	-5.236	55.501	1.00 36.84	AAAA O
ATOM	1420	H	PRO	145	20.318	-3.533	56.859	1.00 45.12	AAAA H
ATOM	1421	CD	PRO	145	20.123	-2.054	57.094	1.00 38.17	AAAA C
ATOM	1422	CA	PRO	145	20.448	-4.233	58.128	1.00 40.19	AAAA C
ATOM	1423	CB	PRO	145	19.704	-3.288	59.099	1.00 37.08	AAAA C
ATOM	1424	CG	PRO	145	20.040	-1.910	58.602	1.00 33.65	AAAA C
ATOM	1425	C	PRO	145	19.993	-5.655	58.155	1.00 47.17	AAAA C
ATOM	1426	O	PRO	145	20.556	-6.592	58.768	1.00 48.05	AAAA O
ATOM	1427	H	LYS	146	18.979	-5.924	57.489	1.00 53.72	AAAA H
ATOM	1429	CA	LYS	146	18.268	-7.029	57.295	1.00 56.94	AAAA C
ATOM	1430	CB	LYS	146	16.894	-7.050	56.647	1.00 65.44	AAAA C
ATOM	1431	CG	LYS	146	16.220	-8.232	55.982	1.00 64.32	AAAA C
ATOM	1432	CD	LYS	146	14.797	-8.422	56.451	0.01 62.75	AAAA C
ATOM	1433	CE	LYS	146	14.194	-9.717	55.934	0.01 62.14	AAAA C
ATOM	1434	HZ	LYS	146	12.700	-9.610	55.753	0.01 61.38	AAAA H
ATOM	1438	C	LYS	146	19.138	-8.138	56.446	1.00 61.40	AAAA C
ATOM	1439	O	LYS	146	19.237	-9.346	56.732	1.00 66.22	AAAA O
ATOM	1440	H	GLU	147	19.779	-7.649	55.399	1.00 62.93	AAAA H
ATOM	1442	CA	GLU	147	20.907	-8.446	54.742	1.00 67.00	AAAA C
ATOM	1443	CB	GLU	147	21.101	-8.070	53.294	1.00 62.32	AAAA C

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ATOM	1444	CD	GLU	147	19.967	-7.579	52.567	1.00	73.15	AAAA C
ATOM	1445	CD	GLU	147	20.164	-7.413	51.093	1.00	85.90	AAAA C
ATOM	1446	OE1	GLU	147	21.339	-7.636	50.701	1.00	95.25	AAAA O
ATOM	1447	OE2	GLU	147	19.291	-7.053	50.376	1.00	87.47	AAAA O
ATOM	1448	C	GLU	147	22.136	-8.470	55.541	1.00	69.40	AAAA C
ATOM	1449	O	GLU	147	22.983	-9.437	55.361	1.00	72.86	AAAA O
ATOM	1450	N	CYS	148	22.506	-7.484	56.355	1.00	66.76	AAAA N
ATOM	1452	CA	CYS	148	23.693	-7.588	57.183	1.00	64.65	AAAA C
ATOM	1453	C	CYS	148	23.598	-8.702	58.196	1.00	65.56	AAAA C
ATOM	1454	O	CYS	148	24.473	-9.524	58.414	1.00	65.89	AAAA O
ATOM	1455	CB	CYS	148	23.952	-6.301	58.001	1.00	57.29	AAAA C
ATOM	1456	SG	CYS	148	24.565	-5.091	56.808	1.00	59.22	AAAA S
ATOM	1457	N	GLY	149	22.514	-8.743	58.977	1.00	67.88	AAAA N
ATOM	1459	CA	GLY	149	22.387	-9.744	60.029	1.00	62.15	AAAA C
ATOM	1460	C	GLY	149	23.443	-9.627	61.120	1.00	59.18	AAAA C
ATOM	1461	O	GLY	149	23.925	-10.603	61.699	1.00	61.11	AAAA O
ATOM	1462	N	ASP	150	23.717	-8.426	61.596	1.00	54.88	AAAA N
ATOM	1464	CA	ASP	150	24.794	-8.198	62.533	1.00	55.78	AAAA C
ATOM	1465	CB	ASP	150	25.041	-6.703	62.750	1.00	49.10	AAAA C
ATOM	1466	CG	ASP	150	25.329	-6.034	61.410	1.00	58.50	AAAA C
ATOM	1467	OD1	ASP	150	25.726	-6.796	60.480	1.00	57.73	AAAA O
ATOM	1468	OD2	ASP	150	25.102	-4.819	61.363	1.00	49.69	AAAA O
ATOM	1469	C	ASP	150	24.519	-8.854	63.855	1.00	59.36	AAAA C
ATOM	1470	O	ASP	150	23.392	-8.820	64.377	1.00	67.48	AAAA O
ATOM	1471	N	LEU	151	25.532	-9.369	64.524	1.00	54.39	AAAA N
ATOM	1473	CA	LEU	151	25.314	-9.908	65.853	1.00	52.79	AAAA C
ATOM	1474	CB	LEU	151	25.208	-11.409	65.806	1.00	58.55	AAAA C
ATOM	1475	CG	LEU	151	24.063	-12.101	65.092	1.00	69.45	AAAA C
ATOM	1476	CD1	LEU	151	24.515	-13.421	64.489	1.00	65.26	AAAA C
ATOM	1477	CD2	LEU	151	22.837	-12.372	65.951	1.00	65.43	AAAA C
ATOM	1478	C	LEU	151	26.409	-9.454	66.805	1.00	51.93	AAAA C
ATOM	1479	O	LEU	151	27.599	-9.734	66.634	1.00	55.59	AAAA O
ATOM	1480	N	CYS	152	26.024	-8.773	67.849	1.00	48.62	AAAA N
ATOM	1482	CA	CYS	152	26.992	-8.189	68.740	1.00	56.73	AAAA C
ATOM	1483	C	CYS	152	27.650	-9.325	69.493	1.00	63.58	AAAA C
ATOM	1484	O	CYS	152	27.074	-10.405	69.575	1.00	62.40	AAAA O
ATOM	1485	CB	CYS	152	26.358	-7.144	69.657	1.00	41.99	AAAA C
ATOM	1486	SG	CYS	152	25.985	-5.635	68.703	1.00	55.83	AAAA S
ATOM	1487	N	PRO	153	28.826	-9.072	70.059	1.00	68.05	AAAA N
ATOM	1488	CD	PRO	153	29.618	-7.838	69.903	1.00	66.66	AAAA C
ATOM	1489	CA	PRO	153	29.497	-10.094	70.851	1.00	70.60	AAAA C
ATOM	1490	CB	PRO	153	30.601	-9.323	71.557	1.00	69.98	AAAA C
ATOM	1491	CG	PRO	153	30.861	-8.159	70.690	1.00	70.58	AAAA C
ATOM	1492	C	PRO	153	28.543	-10.734	71.850	1.00	69.64	AAAA C
ATOM	1493	O	PRO	153	27.859	-10.075	72.615	1.00	69.58	AAAA O
ATOM	1494	N	GLY	154	28.444	-12.049	71.843	1.00	71.23	AAAA N
ATOM	1496	CA	GLY	154	27.610	-12.804	72.745	1.00	78.07	AAAA C
ATOM	1497	C	GLY	154	26.245	-13.230	72.223	1.00	81.75	AAAA C
ATOM	1498	O	GLY	154	25.786	-14.318	72.547	1.00	80.26	AAAA O
ATOM	1499	N	THR	155	25.549	-12.468	71.314	1.00	84.54	AAAA N
ATOM	1501	CA	THR	155	24.314	-12.683	70.828	1.00	89.38	AAAA C
ATOM	1502	CB	THR	155	24.016	-11.661	69.705	1.00	85.07	AAAA C
ATOM	1503	OG1	THR	155	24.063	-10.417	70.420	1.00	84.51	AAAA O
ATOM	1505	CG2	THR	155	22.686	-11.995	69.092	1.00	82.27	AAAA C
ATOM	1506	C	THR	155	24.060	-14.094	70.353	1.00	93.69	AAAA C
ATOM	1507	O	THR	155	23.005	-14.664	70.617	1.00	95.92	AAAA O
ATOM	1508	N	MET	156	25.003	-14.655	69.617	1.00	97.23	AAAA N
ATOM	1510	CA	MET	156	24.884	-15.973	69.024	1.00	99.05	AAAA C
ATOM	1511	CB	MET	156	25.907	-16.190	67.896	1.00	100.40	AAAA C
ATOM	1512	CG	MET	156	25.456	-15.675	66.542	0.01	99.75	AAAA C
ATOM	1513	SD	MET	156	23.687	-15.857	66.255	0.01	99.72	AAAA S
ATOM	1514	CE	MET	156	23.664	-17.214	65.087	0.01	99.59	AAAA C
ATOM	1515	C	MET	156	25.027	-17.106	70.032	1.00	100.57	AAAA C
ATOM	1516	O	MET	156	24.353	-18.122	69.835	1.00	101.64	AAAA O
ATOM	1517	N	ALA	157	25.974	-17.057	70.967	1.00	100.53	AAAA N
ATOM	1519	CA	ALA	157	26.022	-18.192	71.986	1.00	101.00	AAAA C
ATOM	1520	CB	ALA	157	27.317	-18.158	72.766	1.00	103.42	AAAA C
ATOM	1521	C	ALA	157	24.856	-17.890	72.959	1.00	101.10	AAAA C
ATOM	1522	O	ALA	157	23.993	-18.654	72.921	1.00	104.59	AAAA O
ATOM	1523	N	GLU	158	24.984	-16.906	73.841	1.00	98.39	AAAA N
ATOM	1525	CA	GLU	158	23.935	-16.629	74.781	1.00	97.43	AAAA C
ATOM	1526	CB	GLU	158	23.129	-17.865	75.208	1.00	105.93	AAAA C
ATOM	1527	CG	GLU	158	21.587	-17.546	75.560	1.00	113.87	AAAA C
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ATOM	1529	OE1	GLU	158	21.284	-15.733	74.096	1.00	126.20	AAAA O
ATOM	1530	OE2	GLU	158	21.199	-15.317	76.282	1.00	117.79	AAAA O
ATOM	1531	C	GLU	158	24.434	-15.915	76.025	1.00	95.00	AAAA C
ATOM	1532	O	GLU	158	23.988	-16.117	77.145	1.00	95.89	AAAA O
ATOM	1533	N	SER	159	25.276	-14.942	75.769	1.00	93.30	AAAA N
ATOM	1535	CA	SER	159	25.810	-14.119	76.848	1.00	92.28	AAAA C
ATOM	1536	CB	SER	159	26.989	-14.805	77.517	1.00	97.37	AAAA C
ATOM	1537	OG	SER	159	26.972	-14.427	78.886	1.00	98.09	AAAA O
ATOM	1539	C	SER	159	26.228	-12.793	76.326	1.00	91.47	AAAA C
ATOM	1540	O	SER	159	27.368	-12.592	75.810	1.00	92.75	AAAA O
ATOM	1541	N	PRO	160	25.196	-12.007	75.932	1.00	88.65	AAAA N

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ATOM   1542  CD  PRO  160    23.789 -12.122  76.395  1.00 86.67    AAAA C
ATOM   1543  CA  PRO  160    25.463 -10.701  75.361  1.00 84.74    AAAA C
ATOM   1544  CB  PRO  160    24.125  -9.978  75.456  1.00 84.79    AAAA C
ATOM   1545  CG  PRO  160    23.370 -10.671  76.515  1.00 84.62    AAAA C
ATOM   1546  C   PRO  160    26.503 -10.025  76.236  1.00 79.60    AAAA C
ATOM   1547  O   PRO  160    26.319  -9.931  77.456  1.00 79.70    AAAA O
ATOM   1548  N   MET  161    27.563  -9.522  75.596  1.00 74.45    AAAA N
ATOM   1550  CA  MET  161    28.530  -8.735  76.378  1.00 67.04    AAAA C
ATOM   1551  CB  MET  161    29.924  -9.178  76.038  1.00 69.93    AAAA C
ATOM   1552  CG  MET  161    30.118 -10.630  75.706  1.00 71.43    AAAA C
ATOM   1553  SD  MET  161    30.716 -11.621  77.094  1.00 85.25    AAAA S
ATOM   1554  CE  MET  161    29.941 -10.905  78.471  1.00 69.31    AAAA C
ATOM   1555  C   MET  161    28.358  -7.234  76.189  1.00 61.76    AAAA C
ATOM   1556  O   MET  161    28.788  -6.443  77.034  1.00 58.60    AAAA O
ATOM   1557  N   CYS  162    27.681  -6.819  75.095  1.00 54.81    AAAA N
ATOM   1559  CA  CYS  162    27.493  -5.384  74.938  1.00 49.76    AAAA C
ATOM   1560  C   CYS  162    26.306  -4.777  75.670  1.00 51.52    AAAA C
ATOM   1561  O   CYS  162    25.224  -5.324  75.928  1.00 53.89    AAAA O
ATOM   1562  CB  CYS  162    27.422  -5.099  73.459  1.00 48.31    AAAA C
ATOM   1563  SG  CYS  162    28.533  -6.064  72.432  1.00 54.02    AAAA S
ATOM   1564  N   GLU  163    26.409  -3.522  76.031  1.00 46.31    AAAA N
ATOM   1566  CA  GLU  163    25.355  -2.675  76.538  1.00 47.19    AAAA C
ATOM   1567  CB  GLU  163    26.051  -1.412  77.027  1.00 49.95    AAAA C
ATOM   1568  CG  GLU  163    26.476  -1.364  78.465  1.00 62.30    AAAA C
ATOM   1569  CD  GLU  163    25.817  -0.135  79.116  1.00 81.67    AAAA C
ATOM   1570  OE1 GLU  163    26.470   0.473  80.016  1.00 73.22    AAAA O
ATOM   1571  OE2 GLU  163    24.646   0.208  78.721  1.00 80.93    AAAA O
ATOM   1572  C   GLU  163    24.299  -2.340  75.472  1.00 49.05    AAAA C
ATOM   1573  O   GLU  163    24.488  -2.423  74.234  1.00 45.90    AAAA O
ATOM   1574  N   LYS  164    23.142  -1.815  75.880  1.00 47.43    AAAA N
ATOM   1576  CA  LYS  164    22.011  -1.499  75.081  1.00 43.92    AAAA C
ATOM   1577  CB  LYS  164    20.714  -2.244  75.450  1.00 44.48    AAAA C
ATOM   1578  CG  LYS  164    20.560  -3.639  74.870  1.00 48.65    AAAA C
ATOM   1579  CD  LYS  164    19.480  -4.432  75.622  1.00 49.04    AAAA C
ATOM   1580  CE  LYS  164    18.409  -5.012  74.720  1.00 49.21    AAAA C
ATOM   1581  NZ  LYS  164    17.951  -6.372  75.134  1.00 37.67    AAAA N
ATOM   1585  C   LYS  164    21.615  -0.040  75.204  1.00 45.01    AAAA C
ATOM   1586  O   LYS  164    21.466   0.484  76.282  1.00 45.69    AAAA O
ATOM   1587  N   THR  165    21.333   0.570  74.034  1.00 44.94    AAAA N
ATOM   1589  CA  THR  165    20.775   1.943  74.077  1.00 43.13    AAAA C
ATOM   1590  CB  THR  165    21.831   2.952  73.553  1.00 47.81    AAAA C
ATOM   1591  OG1 THR  165    22.053   2.689  72.127  1.00 39.13    AAAA O
ATOM   1593  CG2 THR  165    23.119   2.842  74.362  1.00 40.40    AAAA C
ATOM   1594  C   THR  165    19.532   1.881  73.189  1.00 40.92    AAAA C
ATOM   1595  O   THR  165    19.346   0.897  72.414  1.00 35.91    AAAA O
ATOM   1596  N   THR  166    18.781   2.985  73.173  1.00 39.18    AAAA N
ATOM   1598  CA  THR  166    17.689   2.991  72.182  1.00 42.97    AAAA C
ATOM   1599  CB  THR  166    16.297   3.096  72.833  1.00 55.99    AAAA C
ATOM   1600  OG1 THR  166    15.662   4.385  72.819  1.00 41.42    AAAA O
ATOM   1602  CG2 THR  166    16.157   2.740  74.313  1.00 42.83    AAAA C
ATOM   1603  C   THR  166    17.983   4.051  71.137  1.00 40.17    AAAA C
ATOM   1604  O   THR  166    18.219   5.206  71.509  1.00 35.72    AAAA O
ATOM   1605  N   ILE  167    17.912   3.725  69.866  1.00 42.21    AAAA N
ATOM   1607  CA  ILE  167    18.182   4.672  68.777  1.00 41.05    AAAA C
ATOM   1608  CB  ILE  167    19.437   4.335  67.904  1.00 39.50    AAAA C
ATOM   1609  CG2 ILE  167    19.589   5.346  66.716  1.00 15.26    AAAA C
ATOM   1610  CG1 ILE  167    20.722   4.305  68.724  1.00 36.20    AAAA C
ATOM   1611  CD1 ILE  167    21.899   3.665  67.966  1.00 35.70    AAAA C
ATOM   1612  C   ILE  167    16.937   4.524  67.882  1.00 40.94    AAAA C
ATOM   1613  O   ILE  167    16.655   3.435  67.394  1.00 35.51    AAAA O
ATOM   1614  N   ASN  168    16.318   5.635  67.537  1.00 42.29    AAAA N
ATOM   1616  CA  ASN  168    15.112   5.633  66.713  1.00 45.22    AAAA C
ATOM   1617  CB  ASN  168    15.526   5.253  65.292  1.00 45.69    AAAA C
ATOM   1618  CG  ASN  168    14.497   5.696  64.244  1.00 51.19    AAAA C
ATOM   1619  OD1 ASN  168    14.344   5.112  63.150  1.00 41.75    AAAA O
ATOM   1620  HD2 ASN  168    13.749   6.763  64.522  1.00 48.89    AAAA N
ATOM   1623  C   ASN  168    13.954   4.739  67.141  1.00 46.55    AAAA C
ATOM   1624  O   ASN  168    13.544   3.879  66.326  1.00 45.95    AAAA O
ATOM   1625  N   ASN  169    13.644   4.728  68.433  1.00 45.12    AAAA N
ATOM   1627  CA  ASN  169    12.717   3.759  69.007  1.00 43.67    AAAA C
ATOM   1628  CB  ASN  169    11.315   4.106  68.540  1.00 36.84    AAAA C
ATOM   1629  CG  ASN  169    10.943   5.487  69.093  1.00 42.75    AAAA C
ATOM   1630  OD1 ASN  169    10.917   5.779  70.280  1.00 36.67    AAAA O
ATOM   1631  HD2 ASN  169    10.658   6.448  68.213  1.00 40.74    AAAA N
ATOM   1634  C   ASN  169    13.003   2.306  68.719  1.00 44.69    AAAA C
ATOM   1635  O   ASN  169    12.100   1.544  68.383  1.00 45.72    AAAA O
ATOM   1636  N   GLU  170    14.226   1.907  68.862  1.00 41.64    AAAA N
ATOM   1638  CA  GLU  170    14.655   0.513  68.850  1.00 45.88    AAAA C
ATOM   1639  CB  GLU  170    15.283   0.278  67.524  1.00 55.92    AAAA C
ATOM   1640  CG  GLU  170    15.028  -0.953  66.702  1.00 67.08    AAAA C
ATOM   1641  CD  GLU  170    14.517  -0.605  65.294  1.00 74.56    AAAA C
ATOM   1642  OE1 GLU  170    13.969   0.466  65.049  1.00 77.75    AAAA O
ATOM   1643  OE2 GLU  170    14.763  -1.437  64.389  1.00 70.71    AAAA O
ATOM   1644  C   GLU  170    15.847   0.379  70.019  1.00 47.10    AAAA C
ATOM   1645  O   GLU  170    16.582   1.172  70.213  1.00 49.92    AAAA O
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ATOM	1646	N	TYR	171	15.344	-0.462	70.952	1.00	49.10	AAAA	N
ATOM	1648	CA	TYR	171	16.231	-0.688	72.097	1.00	51.81	AAAA	C
ATOM	1649	CB	TYR	171	15.434	-0.861	73.359	1.00	49.94	AAAA	C
ATOM	1650	CG	TYR	171	16.175	-1.168	74.620	1.00	48.90	AAAA	C
ATOM	1651	CD1	TYR	171	16.980	-0.210	75.237	1.00	46.46	AAAA	C
ATOM	1652	CE1	TYR	171	17.634	-0.469	76.407	1.00	41.17	AAAA	C
ATOM	1653	CD2	TYR	171	16.065	-2.429	75.194	1.00	43.62	AAAA	C
ATOM	1654	CE2	TYR	171	16.734	-2.675	76.366	1.00	44.44	AAAA	C
ATOM	1655	CZ	TYR	171	17.516	-1.718	76.973	1.00	43.58	AAAA	C
ATOM	1656	OH	TYR	171	18.174	-2.017	78.146	1.00	40.16	AAAA	O
ATOM	1658	C	TYR	171	17.058	-1.938	71.830	1.00	51.41	AAAA	C
ATOM	1659	O	TYR	171	16.519	-3.024	71.889	1.00	52.59	AAAA	O
ATOM	1660	N	ASN	172	18.331	-1.752	71.493	1.00	53.70	AAAA	N
ATOM	1662	CA	ASN	172	19.203	-2.898	71.193	1.00	52.36	AAAA	C
ATOM	1663	CB	ASN	172	19.085	-3.278	69.709	1.00	55.43	AAAA	C
ATOM	1664	CG	ASN	172	18.939	-4.766	69.498	1.00	61.75	AAAA	C
ATOM	1665	OD1	ASN	172	19.233	-5.646	70.304	1.00	61.61	AAAA	O
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ATOM	1670	O	ASN	172	21.163	-1.760	72.213	1.00	39.38	AAAA	O
ATOM	1671	N	TYR	173	21.373	-3.796	71.393	1.00	43.20	AAAA	N
ATOM	1673	CA	TYR	173	22.794	-3.929	71.698	1.00	44.76	AAAA	C
ATOM	1674	CB	TYR	173	23.223	-5.374	71.514	1.00	41.66	AAAA	C
ATOM	1675	CG	TYR	173	22.759	-6.274	72.630	1.00	45.18	AAAA	C
ATOM	1676	CD1	TYR	173	21.931	-7.316	72.237	1.00	46.48	AAAA	C
ATOM	1677	CE1	TYR	173	21.438	-8.181	73.193	1.00	51.36	AAAA	C
ATOM	1678	CD2	TYR	173	23.081	-6.132	73.978	1.00	44.86	AAAA	C
ATOM	1679	CE2	TYR	173	22.583	-7.016	74.916	1.00	46.92	AAAA	C
ATOM	1680	CZ	TYR	173	21.757	-8.038	74.535	1.00	50.33	AAAA	C
ATOM	1681	OH	TYR	173	21.171	-9.006	75.328	1.00	50.64	AAAA	O
ATOM	1683	C	TYR	173	23.673	-3.099	70.762	1.00	46.94	AAAA	C
ATOM	1684	O	TYR	173	23.389	-2.983	69.567	1.00	49.76	AAAA	O
ATOM	1685	N	ARG	174	24.579	-2.318	71.366	1.00	47.79	AAAA	N
ATOM	1687	CA	ARG	174	25.517	-1.496	70.577	1.00	49.13	AAAA	C
ATOM	1688	CB	ARG	174	25.537	-0.132	71.233	1.00	44.32	AAAA	C
ATOM	1689	CG	ARG	174	24.210	0.623	71.234	1.00	48.14	AAAA	C
ATOM	1690	CD	ARG	174	23.372	0.344	70.003	1.00	51.47	AAAA	C
ATOM	1691	NE	ARG	174	21.974	0.760	70.039	1.00	48.35	AAAA	N
ATOM	1693	CZ	ARG	174	21.144	0.570	69.017	1.00	48.23	AAAA	C
ATOM	1694	NH1	ARG	174	21.477	0.022	67.864	1.00	38.96	AAAA	N
ATOM	1697	NH2	ARG	174	19.909	1.022	69.197	1.00	54.65	AAAA	N
ATOM	1700	C	ARG	174	26.921	-2.094	70.461	1.00	45.98	AAAA	C
ATOM	1701	O	ARG	174	27.548	-2.557	71.406	1.00	44.97	AAAA	O
ATOM	1702	N	CYS	175	27.493	-2.183	69.294	1.00	46.21	AAAA	N
ATOM	1704	CA	CYS	175	28.787	-2.758	68.997	1.00	45.60	AAAA	C
ATOM	1705	C	CYS	175	29.407	-2.395	67.665	1.00	46.23	AAAA	C
ATOM	1706	O	CYS	175	28.755	-2.018	66.665	1.00	44.78	AAAA	O
ATOM	1707	CB	CYS	175	28.576	-4.253	69.167	1.00	35.62	AAAA	C
ATOM	1708	SG	CYS	175	27.812	-5.181	67.807	1.00	51.92	AAAA	S
ATOM	1709	N	TRP	176	30.764	-2.517	67.583	1.00	48.16	AAAA	N
ATOM	1711	CA	TRP	176	31.430	-2.091	66.325	1.00	42.48	AAAA	C
ATOM	1712	CB	TRP	176	32.769	-1.409	66.564	1.00	36.38	AAAA	C
ATOM	1713	CG	TRP	176	32.680	-0.069	67.203	1.00	25.56	AAAA	C
ATOM	1714	CD2	TRP	176	32.588	1.186	66.480	1.00	23.71	AAAA	C
ATOM	1715	CE2	TRP	176	32.599	2.217	67.422	1.00	30.40	AAAA	C
ATOM	1716	CE3	TRP	176	32.535	1.520	65.141	1.00	24.31	AAAA	C
ATOM	1717	CD1	TRP	176	32.730	0.257	68.525	1.00	28.37	AAAA	C
ATOM	1718	NE1	TRP	176	32.636	1.636	68.678	1.00	37.21	AAAA	N
ATOM	1720	CZ2	TRP	176	32.441	3.565	67.088	1.00	28.51	AAAA	C
ATOM	1721	CZ3	TRP	176	32.447	2.822	64.789	1.00	22.23	AAAA	C
ATOM	1722	CH2	TRP	176	32.406	3.817	65.745	1.00	29.51	AAAA	C
ATOM	1723	C	TRP	176	31.631	-3.268	65.408	1.00	39.30	AAAA	C
ATOM	1724	O	TRP	176	31.703	-3.121	64.199	1.00	39.15	AAAA	O
ATOM	1725	N	THR	177	31.682	-4.460	66.005	1.00	41.33	AAAA	N
ATOM	1727	CA	THR	177	31.964	-5.644	65.161	1.00	49.28	AAAA	C
ATOM	1728	CB	THR	177	33.480	-6.062	65.162	1.00	43.66	AAAA	C
ATOM	1729	OG1	THR	177	34.309	-5.025	64.615	1.00	47.85	AAAA	O
ATOM	1731	CG2	THR	177	33.676	-7.271	64.283	1.00	58.51	AAAA	C
ATOM	1732	C	THR	177	31.290	-6.814	65.858	1.00	48.76	AAAA	C
ATOM	1733	O	THR	177	30.982	-6.539	67.001	1.00	51.53	AAAA	O
ATOM	1734	N	THR	178	31.269	-8.000	65.331	1.00	51.96	AAAA	N
ATOM	1736	CA	THR	178	30.924	-9.236	65.948	1.00	58.95	AAAA	C
ATOM	1737	CB	THR	178	31.253	-10.500	65.082	1.00	66.55	AAAA	C
ATOM	1738	OG1	THR	178	31.505	-10.066	63.734	1.00	75.76	AAAA	O
ATOM	1740	CG2	THR	178	30.104	-11.489	65.148	1.00	74.23	AAAA	C
ATOM	1741	C	THR	178	31.714	-9.539	67.213	1.00	60.25	AAAA	C
ATOM	1742	O	THR	178	31.204	-10.202	68.135	1.00	66.05	AAAA	O
ATOM	1743	N	ASN	179	32.977	-9.130	67.293	1.00	57.56	AAAA	N
ATOM	1745	CA	ASN	179	33.793	-9.392	68.443	1.00	53.39	AAAA	C
ATOM	1746	CB	ASN	179	35.130	-10.024	68.068	1.00	48.46	AAAA	C
ATOM	1747	CG	ASN	179	34.997	-11.218	67.126	1.00	56.25	AAAA	C
ATOM	1748	OD1	ASN	179	34.412	-12.291	67.553	1.00	51.38	AAAA	O
ATOM	1749	ND2	ASN	179	35.229	-11.063	65.863	1.00	48.10	AAAA	N
ATOM	1752	C	ASN	179	34.096	-8.190	69.295	1.00	50.78	AAAA	C
ATOM	1753	O	ASN	179	34.556	-8.377	70.420	1.00	57.97	AAAA	O

ATOM	1754	H	ARG	180	33.626	-7.022	68.913	1.00	47.06	AAAA N
ATOM	1756	CA	ARG	180	33.808	-5.820	69.691	1.00	48.25	AAAA C
ATOM	1757	CB	ARG	180	34.925	-4.962	69.074	1.00	49.72	AAAA C
ATOM	1758	CG	ARG	180	36.324	-5.501	69.285	1.00	60.92	AAAA C
ATOM	1759	CD	ARG	180	37.288	-4.948	68.279	1.00	70.83	AAAA C
ATOM	1760	NE	ARG	180	38.569	-5.605	68.203	1.00	76.18	AAAA N
ATOM	1762	CZ	ARG	180	39.298	-5.895	69.276	1.00	76.59	AAAA C
ATOM	1763	NH1	ARG	180	38.877	-5.608	70.498	1.00	80.82	AAAA N
ATOM	1766	NH2	ARG	180	40.474	-6.478	69.190	1.00	79.33	AAAA N
ATOM	1769	C	ARG	180	32.530	-4.977	69.821	1.00	48.10	AAAA C
ATOM	1770	O	ARG	180	31.862	-4.476	68.905	1.00	46.99	AAAA O
ATOM	1771	N	CYS	181	32.230	-4.728	71.063	1.00	44.80	AAAA N
ATOM	1773	CA	CYS	181	31.199	-3.924	71.619	1.00	45.20	AAAA C
ATOM	1774	C	CYS	181	31.646	-2.463	71.692	1.00	44.50	AAAA C
ATOM	1775	O	CYS	181	32.835	-2.227	71.724	1.00	47.09	AAAA O
ATOM	1776	CB	CYS	181	30.940	-4.282	73.110	1.00	43.88	AAAA C
ATOM	1777	SG	CYS	181	30.363	-5.944	73.316	1.00	56.08	AAAA S
ATOM	1778	N	GLN	182	30.659	-1.600	71.690	1.00	39.30	AAAA N
ATOM	1780	CA	GLN	182	30.948	-0.177	71.690	1.00	43.43	AAAA C
ATOM	1781	CB	GLN	182	29.749	0.619	71.196	1.00	23.99	AAAA C
ATOM	1782	CG	GLN	182	29.809	2.085	71.435	1.00	28.57	AAAA C
ATOM	1783	CD	GLN	182	28.757	2.867	70.733	1.00	29.35	AAAA C
ATOM	1784	OE1	GLN	182	27.898	2.304	70.033	1.00	38.55	AAAA O
ATOM	1785	NE2	GLN	182	28.857	4.164	70.912	1.00	28.14	AAAA N
ATOM	1788	C	GLN	182	31.218	0.089	73.162	1.00	46.07	AAAA C
ATOM	1789	O	GLN	182	30.458	-0.327	74.041	1.00	47.01	AAAA O
ATOM	1790	N	LYS	183	32.213	0.866	73.524	1.00	46.98	AAAA N
ATOM	1792	CA	LYS	183	32.479	1.064	74.934	1.00	45.26	AAAA C
ATOM	1793	CB	LYS	183	33.966	1.275	75.185	1.00	48.68	AAAA C
ATOM	1794	CG	LYS	183	34.865	0.267	74.482	1.00	47.95	AAAA C
ATOM	1795	CD	LYS	183	36.337	0.734	74.523	1.00	48.06	AAAA C
ATOM	1796	CE	LYS	183	37.178	-0.208	73.684	1.00	46.78	AAAA C
ATOM	1797	NZ	LYS	183	38.499	-0.654	74.158	1.00	44.00	AAAA N
ATOM	1801	C	LYS	183	31.659	2.205	75.477	1.00	48.13	AAAA C
ATOM	1802	O	LYS	183	31.679	3.305	74.946	1.00	48.84	AAAA O
ATOM	1803	N	MET	184	31.165	2.014	76.698	1.00	52.59	AAAA N
ATOM	1805	CA	MET	184	30.388	3.041	77.413	1.00	53.22	AAAA C
ATOM	1806	CB	MET	184	28.927	2.613	77.537	1.00	54.27	AAAA C
ATOM	1807	CG	MET	184	27.855	2.955	76.536	1.00	56.16	AAAA C
ATOM	1808	SD	MET	184	26.911	1.601	75.912	1.00	57.56	AAAA S
ATOM	1809	CE	MET	184	26.738	1.855	74.171	1.00	46.57	AAAA C
ATOM	1810	C	MET	184	31.051	3.200	78.770	1.00	50.55	AAAA C
ATOM	1811	O	MET	184	31.770	2.292	79.116	1.00	48.82	AAAA O
ATOM	1812	N	CYS	185	30.796	4.195	79.565	1.00	53.97	AAAA N
ATOM	1814	CA	CYS	185	31.342	4.365	80.892	1.00	58.63	AAAA C
ATOM	1815	C	CYS	185	30.297	4.320	81.989	1.00	65.16	AAAA C
ATOM	1816	O	CYS	185	29.133	4.649	81.761	1.00	65.87	AAAA O
ATOM	1817	CB	CYS	185	31.965	5.772	81.000	1.00	60.37	AAAA C
ATOM	1818	SG	CYS	185	33.623	5.771	80.312	1.00	60.09	AAAA S
ATOM	1819	N	PRO	186	30.688	3.978	83.206	1.00	69.41	AAAA N
ATOM	1820	CD	PRO	186	32.066	3.777	83.702	1.00	71.11	AAAA C
ATOM	1821	CA	PRO	186	29.717	3.933	84.304	1.00	69.11	AAAA C
ATOM	1822	CB	PRO	186	30.523	3.487	85.503	1.00	68.03	AAAA C
ATOM	1823	CG	PRO	186	31.910	3.920	85.198	1.00	71.02	AAAA C
ATOM	1824	C	PRO	186	29.120	5.320	84.431	1.00	69.47	AAAA C
ATOM	1825	O	PRO	186	29.820	6.345	84.507	1.00	65.93	AAAA O
ATOM	1826	N	SER	187	27.801	5.367	84.546	1.00	68.78	AAAA N
ATOM	1828	CA	SER	187	27.050	6.592	84.750	1.00	69.29	AAAA C
ATOM	1829	CB	SER	187	25.594	6.287	85.129	1.00	78.29	AAAA C
ATOM	1830	OG	SER	187	25.474	4.935	85.563	1.00	91.78	AAAA O
ATOM	1832	C	SER	187	27.630	7.476	85.836	1.00	67.19	AAAA C
ATOM	1833	O	SER	187	27.606	8.708	85.803	1.00	63.98	AAAA O
ATOM	1834	N	THR	188	28.108	6.853	86.908	1.00	68.20	AAAA N
ATOM	1836	CA	THR	188	28.870	7.507	87.963	1.00	68.39	AAAA C
ATOM	1837	CB	THR	188	29.805	6.459	88.618	1.00	73.84	AAAA C
ATOM	1838	OG1	THR	188	28.943	5.365	89.016	1.00	89.33	AAAA O
ATOM	1840	CG2	THR	188	30.605	7.048	89.759	1.00	73.71	AAAA C
ATOM	1841	C	THR	188	29.802	8.583	87.429	1.00	67.92	AAAA C
ATOM	1842	O	THR	188	29.843	9.739	87.834	1.00	68.30	AAAA O
ATOM	1843	N	CYS	189	30.643	8.247	86.446	1.00	63.89	AAAA N
ATOM	1845	CA	CYS	189	31.583	9.116	85.817	1.00	57.29	AAAA C
ATOM	1846	C	CYS	189	30.951	10.331	85.195	1.00	57.70	AAAA C
ATOM	1847	O	CYS	189	31.648	11.327	85.017	1.00	57.56	AAAA O
ATOM	1848	CB	CYS	189	32.416	8.372	84.769	1.00	58.67	AAAA C
ATOM	1849	SG	CYS	189	33.347	7.001	85.535	1.00	53.46	AAAA S
ATOM	1850	N	GLY	190	29.689	10.322	84.806	1.00	56.91	AAAA N
ATOM	1852	CA	GLY	190	29.038	11.521	84.323	1.00	57.28	AAAA C
ATOM	1853	C	GLY	190	29.444	11.834	82.886	1.00	59.62	AAAA C
ATOM	1854	O	GLY	190	29.609	10.932	82.082	1.00	57.91	AAAA O
ATOM	1855	N	LYS	191	29.842	13.052	82.624	1.00	62.78	AAAA N
ATOM	1857	CA	LYS	191	30.359	13.520	81.364	1.00	67.72	AAAA C
ATOM	1858	CB	LYS	191	30.058	15.035	81.214	1.00	72.76	AAAA C
ATOM	1859	CG	LYS	191	28.568	15.288	81.002	1.00	84.69	AAAA C
ATOM	1860	CD	LYS	191	28.207	16.733	80.723	1.00	90.15	AAAA C
ATOM	1861	CE	LYS	191	26.713	16.806	80.471	1.00	91.93	AAAA C

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ATOM   1862  HZ   LYS  191    26.368  16.182  79.152  1.00 97.62   AAAA  H
ATOM   1866  C    LYS  191    31.868  13.299  81.270  1.00 70.13   AAAA  C
ATOM   1867  O    LYS  191    32.486  13.935  80.415  1.00 71.76   AAAA  O
ATOM   1868  N    ARG  192    32.488  12.441  82.079  1.00 66.29   AAAA  N
ATOM   1870  CA   ARG  192    33.885  12.171  82.044  1.00 59.95   AAAA  C
ATOM   1871  CB   ARG  192    34.505  12.070  83.432  1.00 66.58   AAAA  C
ATOM   1872  CG   ARG  192    34.679  13.400  84.131  1.00 71.59   AAAA  C
ATOM   1873  CD   ARG  192    34.386  13.330  85.625  1.00 73.91   AAAA  C
ATOM   1874  HE   ARG  192    35.622  13.280  86.377  1.00 85.74   AAAA  H
ATOM   1876  CZ   ARG  192    35.968  12.407  87.330  1.00 90.67   AAAA  C
ATOM   1877  NH1  ARG  192    35.026  11.486  87.600  1.00 88.49   AAAA  N
ATOM   1880  NH2  ARG  192    37.162  12.463  87.950  1.00 72.95   AAAA  N
ATOM   1883  C    ARG  192    34.221  10.851  81.337  1.00 58.83   AAAA  C
ATOM   1884  O    ARG  192    33.336  10.007  81.176  1.00 55.13   AAAA  O
ATOM   1885  N    ALA  193    35.521  10.795  80.968  1.00 50.19   AAAA  N
ATOM   1887  CA   ALA  193    35.962   9.557  80.355  1.00 46.24   AAAA  C
ATOM   1888  CB   ALA  193    37.167   9.921  79.541  1.00 45.15   AAAA  C
ATOM   1889  C    ALA  193    36.221   8.525  81.451  1.00 48.97   AAAA  C
ATOM   1890  O    ALA  193    36.220   8.908  82.616  1.00 44.80   AAAA  O
ATOM   1891  N    CYS  194    36.544   7.304  81.065  1.00 50.30   AAAA  N
ATOM   1893  CA   CYS  194    36.836   6.302  82.043  1.00 57.50   AAAA  C
ATOM   1894  C    CYS  194    37.834   5.304  81.448  1.00 61.25   AAAA  C
ATOM   1895  O    CYS  194    37.952   5.291  80.216  1.00 61.52   AAAA  O
ATOM   1896  CB   CYS  194    35.510   5.741  82.504  1.00 57.96   AAAA  C
ATOM   1897  SG   CYS  194    34.785   4.524  81.402  1.00 54.49   AAAA  S
ATOM   1898  N    THR  195    38.422   4.499  82.311  1.00 58.51   AAAA  N
ATOM   1900  CA   THR  195    39.462   3.584  81.913  1.00 57.42   AAAA  C
ATOM   1901  CB   THR  195    40.237   3.142  83.188  1.00 65.73   AAAA  C
ATOM   1902  OG1  THR  195    40.288   4.248  84.091  1.00 70.15   AAAA  O
ATOM   1904  CG2  THR  195    41.684   2.864  82.745  1.00 77.91   AAAA  C
ATOM   1905  C    THR  195    38.857   2.404  81.226  1.00 54.59   AAAA  C
ATOM   1906  O    THR  195    37.633   2.315  81.319  1.00 58.75   AAAA  O
ATOM   1907  N    GLU  196    39.610   1.408  80.882  1.00 55.95   AAAA  N
ATOM   1909  CA   GLU  196    39.139   0.145  80.364  1.00 60.07   AAAA  C
ATOM   1910  CB   GLU  196    40.395  -0.612  79.914  1.00 68.06   AAAA  C
ATOM   1911  CG   GLU  196    40.479  -1.146  78.526  1.00 73.96   AAAA  C
ATOM   1912  CD   GLU  196    39.235  -0.983  77.670  1.00 83.08   AAAA  C
ATOM   1913  OE1  GLU  196    38.356  -1.884  77.687  1.00 81.19   AAAA  O
ATOM   1914  OE2  GLU  196    39.060   0.041  76.939  1.00 82.10   AAAA  O
ATOM   1915  C    GLU  196    38.382  -0.579  81.467  1.00 63.91   AAAA  C
ATOM   1916  O    GLU  196    37.690  -1.537  81.159  1.00 63.51   AAAA  O
ATOM   1917  N    ASN  197    38.666  -0.312  82.739  1.00 67.40   AAAA  N
ATOM   1919  CA   ASN  197    38.025  -0.947  83.886  1.00 69.21   AAAA  C
ATOM   1920  CB   ASN  197    39.021  -1.394  84.966  1.00 68.49   AAAA  C
ATOM   1921  CG   ASN  197    39.722  -2.692  84.672  0.01 69.09   AAAA  C
ATOM   1922  OD1  ASN  197    40.364  -3.273  85.551  0.01 69.04   AAAA  O
ATOM   1923  ND2  ASN  197    39.622  -3.183  83.443  0.01 68.97   AAAA  N
ATOM   1926  C    ASN  197    37.033   0.043  84.486  1.00 69.01   AAAA  C
ATOM   1927  O    ASN  197    36.845   0.281  85.664  1.00 68.24   AAAA  O
ATOM   1928  N    ASN  198    36.384   0.795  83.607  1.00 69.91   AAAA  N
ATOM   1930  CA   ASN  198    35.356   1.734  84.048  1.00 68.48   AAAA  C
ATOM   1931  CB   ASN  198    34.120   0.880  84.373  1.00 66.12   AAAA  C
ATOM   1932  CG   ASN  198    33.806   0.095  83.102  1.00 69.29   AAAA  C
ATOM   1933  OD1  ASN  198    33.475   0.654  82.054  1.00 73.20   AAAA  O
ATOM   1934  ND2  ASN  198    33.980  -1.206  83.268  1.00 65.34   AAAA  N
ATOM   1937  C    ASN  198    35.784   2.563  85.228  1.00 64.01   AAAA  C
ATOM   1938  O    ASN  198    34.992   2.827  86.117  1.00 64.20   AAAA  O
ATOM   1939  N    GLU  199    36.955   3.164  85.157  1.00 64.75   AAAA  N
ATOM   1941  CA   GLU  199    37.342   4.054  86.255  1.00 64.64   AAAA  C
ATOM   1942  CB   GLU  199    38.702   3.624  86.744  1.00 66.11   AAAA  C
ATOM   1943  CG   GLU  199    38.846   3.717  88.233  1.00 77.15   AAAA  C
ATOM   1944  CD   GLU  199    39.579   2.532  88.832  1.00 80.24   AAAA  C
ATOM   1945  OE1  GLU  199    39.385   2.406  90.066  1.00 81.65   AAAA  O
ATOM   1946  OE2  GLU  199    40.282   1.821  88.079  1.00 77.94   AAAA  O
ATOM   1947  C    GLU  199    37.314   5.463  85.690  1.00 62.92   AAAA  C
ATOM   1948  O    GLU  199    37.922   5.676  84.632  1.00 63.62   AAAA  O
ATOM   1949  N    CYS  200    36.605   6.393  86.313  1.00 56.16   AAAA  N
ATOM   1951  CA   CYS  200    36.600   7.721  85.740  1.00 55.11   AAAA  C
ATOM   1952  C    CYS  200    37.978   8.315  85.521  1.00 57.77   AAAA  C
ATOM   1953  O    CYS  200    38.884   8.058  86.300  1.00 63.79   AAAA  O
ATOM   1954  CB   CYS  200    35.824   8.664  86.648  1.00 52.70   AAAA  C
ATOM   1955  SG   CYS  200    34.196   8.100  87.098  1.00 55.85   AAAA  S
ATOM   1956  N    CYS  201    38.124   9.192  84.549  1.00 54.50   AAAA  N
ATOM   1958  CA   CYS  201    39.338   9.889  84.202  1.00 48.19   AAAA  C
ATOM   1959  C    CYS  201    39.236  11.287  84.786  1.00 42.34   AAAA  C
ATOM   1960  O    CYS  201    38.165  11.704  85.166  1.00 54.32   AAAA  O
ATOM   1961  CB   CYS  201    39.590  10.070  82.695  1.00 40.90   AAAA  C
ATOM   1962  SG   CYS  201    39.644   8.597  81.747  1.00 51.42   AAAA  S
ATOM   1963  N    HIS  202    40.254  12.075  84.675  1.00 39.12   AAAA  N
ATOM   1965  CA   HIS  202    40.290  13.461  85.128  1.00 41.55   AAAA  C
ATOM   1966  C    HIS  202    39.284  14.184  84.289  1.00 46.59   AAAA  C
ATOM   1967  O    HIS  202    39.176  13.851  83.103  1.00 51.64   AAAA  O
ATOM   1968  CB   HIS  202    41.712  13.952  84.810  1.00 45.20   AAAA  C
ATOM   1969  CG   HIS  202    41.996  15.330  85.267  1.00 39.71   AAAA  C
ATOM   1970  ND1  HIS  202    41.501  16.404  84.550  1.00 51.32   AAAA  N
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ATOM    1971   CE1 HIS   202    41.887   17.528   85.178   1.00 47.60   AAAA C
ATOM    1972   CD2 HIS   202    42.665   15.813   86.340   1.00 39.59   AAAA C
ATOM    1973   NE2 HIS   202    42.563   17.207   86.258   1.00 43.48   AAAA N
ATOM    1975   N   PRO   203    38.738   15.293   84.711   1.00 47.74   AAAA N
ATOM    1976   CD  PRO   203    38.758   15.840   86.082   1.00 46.97   AAAA C
ATOM    1977   CA  PRO   203    37.780   15.987   83.879   1.00 46.44   AAAA C
ATOM    1978   CB  PRO   203    37.248   17.107   84.742   1.00 39.47   AAAA C
ATOM    1979   CG  PRO   203    38.131   17.210   85.910   1.00 43.37   AAAA C
ATOM    1980   C   PRO   203    38.440   16.519   82.607   1.00 53.27   AAAA C
ATOM    1981   O   PRO   203    37.698   17.045   81.731   1.00 53.16   AAAA O
ATOM    1982   N   GLU   204    39.792   16.535   82.561   1.00 50.34   AAAA N
ATOM    1984   CA  GLU   204    40.439   17.139   91.382   1.00 50.52   AAAA C
ATOM    1985   CB  GLU   204    41.727   17.891   81.804   1.00 48.58   AAAA C
ATOM    1996   CG  GLU   204    41.397   19.251   82.397   1.00 43.74   AAAA C
ATOM    1387   CD  GLU   204    40.778   20.282   81.501   1.00 55.26   AAAA C
ATOM    1988   OE1 GLU   204    40.766   20.344   80.248   1.00 64.04   AAAA O
ATOM    1989   OE2 GLU   204    40.226   21.198   82.141   1.00 57.66   AAAA O
ATOM    1990   C   GLU   204    40.718   16.084   80.319   1.00 45.71   AAAA C
ATOM    1991   O   GLU   204    41.238   16.405   79.251   1.00 46.56   AAAA O
ATOM    1992   N   CYS   205    40.612   14.830   80.735   1.00 42.05   AAAA N
ATOM    1994   CA  CYS   205    40.997   13.764   79.838   1.00 45.81   AAAA C
ATOM    1995   C   CYS   205    39.892   13.628   78.819   1.00 49.20   AAAA C
ATOM    1996   O   CYS   205    38.746   13.920   79.133   1.00 50.34   AAAA O
ATOM    1997   CB  CYS   205    41.288   12.491   80.572   1.00 51.55   AAAA C
ATOM    1998   SG  CYS   205    42.923   12.246   81.251   1.00 52.89   AAAA S
ATOM    1999   N   LEU   206    40.232   13.579   77.520   1.00 49.88   AAAA N
ATOM    2001   CA  LEU   206    39.169   13.446   76.533   1.00 41.49   AAAA C
ATOM    2002   CB  LEU   206    39.266   14.505   75.462   1.00 48.66   AAAA C
ATOM    2003   CG  LEU   206    38.274   14.365   74.305   1.00 47.45   AAAA C
ATOM    2004   CD1 LEU   206    36.879   14.243   74.895   1.00 45.79   AAAA C
ATOM    2005   CD2 LEU   206    38.331   15.599   73.420   1.00 50.71   AAAA C
ATOM    2006   C   LEU   206    39.310   12.109   75.912   1.00 38.44   AAAA C
ATOM    2007   O   LEU   206    40.400   11.568   75.813   1.00 36.59   AAAA O
ATOM    2008   N   GLY   207    38.264   11.359   75.681   1.00 42.41   AAAA N
ATOM    2010   CA  GLY   207    38.403   10.098   74.978   1.00 40.57   AAAA C
ATOM    2011   C   GLY   207    38.466    9.061   76.058   1.00 47.15   AAAA C
ATOM    2012   O   GLY   207    37.668    8.102   76.057   1.00 45.04   AAAA O
ATOM    2013   N   SER   208    39.622    9.079   76.760   1.00 50.36   AAAA N
ATOM    2015   CA  SER   208    39.832    7.898   77.660   1.00 48.27   AAAA C
ATOM    2016   CB  SER   208    39.909    6.631   76.787   1.00 35.77   AAAA C
ATOM    2017   OG  SER   208    40.600    5.597   77.461   1.00 61.34   AAAA O
ATOM    2019   C   SER   208    41.144    8.068   78.377   1.00 49.17   AAAA C
ATOM    2020   O   SER   208    41.781    9.084   78.163   1.00 48.24   AAAA O
ATOM    2021   N   CYS   209    41.599    7.123   79.189   1.00 52.04   AAAA N
ATOM    2023   CA  CYS   209    42.824    7.307   79.964   1.00 55.98   AAAA C
ATOM    2024   C   CYS   209    43.453    6.035   80.484   1.00 57.41   AAAA C
ATOM    2025   O   CYS   209    42.862    4.963   80.423   1.00 58.33   AAAA O
ATOM    2026   CB  CYS   209    42.629    8.258   81.146   1.00 52.51   AAAA C
ATOM    2027   SG  CYS   209    41.380    7.602   82.261   1.00 58.22   AAAA S
ATOM    2028   N   SER   210    44.734    6.145   80.883   1.00 59.37   AAAA N
ATOM    2030   CA  SER   210    45.506    4.950   81.318   1.00 59.10   AAAA C
ATOM    2031   CB  SER   210    47.022    5.083   81.105   1.00 55.07   AAAA C
ATOM    2032   OG  SER   210    47.546    6.204   81.819   1.00 64.49   AAAA O
ATOM    2034   C   SER   210    45.331    4.713   82.826   1.00 56.34   AAAA C
ATOM    2035   O   SER   210    45.529    3.614   83.326   1.00 54.42   AAAA O
ATOM    2036   N   ALA   211    45.105    5.806   83.548   1.00 52.79   AAAA N
ATOM    2038   CA  ALA   211    44.980    5.684   85.004   1.00 56.60   AAAA C
ATOM    2039   CB  ALA   211    46.333    5.926   85.649   1.00 63.41   AAAA C
ATOM    2040   C   ALA   211    43.962    6.747   85.395   1.00 56.58   AAAA C
ATOM    2041   O   ALA   211    43.957    7.792   84.711   1.00 50.78   AAAA O
ATOM    2042   N   PRO   212    43.117    6.416   86.359   1.00 55.93   AAAA N
ATOM    2043   CD  PRO   212    43.042    5.166   87.115   1.00 55.86   AAAA C
ATOM    2044   CA  PRO   212    41.951    7.257   86.575   1.00 55.50   AAAA C
ATOM    2045   CB  PRO   212    41.104    6.470   87.556   1.00 59.65   AAAA C
ATOM    2046   CG  PRO   212    42.021    5.483   88.175   1.00 51.56   AAAA C
ATOM    2047   C   PRO   212    42.409    8.535   87.177   1.00 53.64   AAAA C
ATOM    2048   O   PRO   212    43.611    8.725   87.393   1.00 57.48   AAAA O
ATOM    2049   N   ALA   213    41.537    9.492   87.347   1.00 53.87   AAAA N
ATOM    2051   CA  ALA   213    41.912   10.710   88.057   1.00 59.41   AAAA C
ATOM    2052   CB  ALA   213    41.783   10.255   89.541   1.00 66.40   AAAA C
ATOM    2053   C   ALA   213    43.289   11.300   87.907   1.00 61.40   AAAA C
ATOM    2054   O   ALA   213    43.729   12.202   88.652   1.00 60.03   AAAA O
ATOM    2055   N   ASN   214    44.068   10.999   86.899   1.00 64.80   AAAA N
ATOM    2057   CA  ASN   214    45.366   11.551   86.596   1.00 63.36   AAAA C
ATOM    2063   C   ASN   214    45.300   12.284   85.251   1.00 61.56   AAAA C
ATOM    2064   O   ASN   214    45.198   11.794   84.117   1.00 58.38   AAAA O
ATOM    2058   CB  ASN   214    46.336   10.379   86.608   1.00 67.32   AAAA C
ATOM    2059   CG  ASN   214    47.697   10.896   86.362   1.00 75.48   AAAA C
ATOM    2060   OD1 ASN   214    48.254   11.105   85.302   1.00 83.64   AAAA O
ATOM    2061   HD2 ASN   214    48.513   11.170   87.427   1.00 90.05   AAAA N
ATOM    2065   N   ASP   215    45.666   13.565   85.305   1.00 59.78   AAAA N
ATOM    2067   CA  ASP   215    45.618   14.432   84.143   1.00 56.47   AAAA C
ATOM    2068   CB  ASP   215    45.430   15.926   84.446   1.00 40.19   AAAA C
ATOM    2069   CG  ASP   215    46.671   16.543   84.986   1.00 56.36   AAAA C
ATOM    2070   OD1 ASP   215    46.590   17.699   85.473   1.00 56.17   AAAA O
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ATOM	2071	OD2	ASP	215	47.766	15.926	84.941	1.00	60.01	AAAA	O
ATOM	2072	C	ASP	215	46.819	14.315	83.221	1.00	53.78	AAAA	C
ATOM	2073	O	ASP	215	46.998	15.148	82.322	1.00	53.58	AAAA	O
ATOM	2074	N	THR	216	47.719	13.425	83.511	1.00	50.87	AAAA	N
ATOM	2076	CA	THR	216	48.883	13.114	82.734	1.00	45.76	AAAA	C
ATOM	2077	CB	THR	216	50.201	13.176	83.529	1.00	53.46	AAAA	C
ATOM	2078	OG1	THR	216	50.403	11.977	84.335	1.00	45.14	AAAA	O
ATOM	2080	CG2	THR	216	50.436	14.314	84.518	1.00	41.38	AAAA	C
ATOM	2081	C	THR	216	48.681	11.712	82.158	1.00	48.34	AAAA	C
ATOM	2082	O	THR	216	49.596	11.282	81.444	1.00	47.49	AAAA	O
ATOM	2083	N	ALA	217	47.553	11.057	82.476	1.00	49.65	AAAA	N
ATOM	2085	CA	ALA	217	47.259	9.760	81.845	1.00	51.83	AAAA	C
ATOM	2086	CB	ALA	217	46.998	9.775	82.943	1.00	52.62	AAAA	C
ATOM	2087	C	ALA	217	46.207	9.747	80.709	1.00	50.60	AAAA	C
ATOM	2088	O	ALA	217	45.775	8.632	80.335	1.00	49.13	AAAA	O
ATOM	2089	N	CYS	218	45.744	10.905	80.226	1.00	43.56	AAAA	N
ATOM	2091	CA	CYS	218	44.802	11.030	79.157	1.00	48.09	AAAA	C
ATOM	2092	C	CYS	218	45.166	10.331	77.869	1.00	47.06	AAAA	C
ATOM	2093	O	CYS	218	46.300	9.967	77.642	1.00	55.57	AAAA	O
ATOM	2094	CB	CYS	218	44.536	12.501	78.775	1.00	51.54	AAAA	C
ATOM	2095	SG	CYS	218	44.256	13.494	80.302	1.00	56.98	AAAA	S
ATOM	2096	N	VAL	219	44.226	10.085	76.978	1.00	43.40	AAAA	N
ATOM	2098	CA	VAL	219	44.575	9.547	75.654	1.00	35.22	AAAA	C
ATOM	2099	CB	VAL	219	43.693	8.427	75.242	1.00	32.26	AAAA	C
ATOM	2100	CG1	VAL	219	43.952	7.873	73.886	1.00	36.19	AAAA	C
ATOM	2101	CG2	VAL	219	43.811	7.144	76.071	1.00	45.51	AAAA	C
ATOM	2102	C	VAL	219	44.453	10.750	74.735	1.00	32.06	AAAA	C
ATOM	2103	O	VAL	219	45.303	10.897	73.874	1.00	42.27	AAAA	O
ATOM	2104	N	ALA	220	43.729	11.753	75.187	1.00	24.24	AAAA	N
ATOM	2106	CA	ALA	220	43.639	12.985	74.385	1.00	27.99	AAAA	C
ATOM	2107	CB	ALA	220	42.536	12.919	73.331	1.00	28.42	AAAA	C
ATOM	2108	C	ALA	220	43.292	14.071	75.390	1.00	29.21	AAAA	C
ATOM	2109	O	ALA	220	42.846	13.604	76.455	1.00	37.88	AAAA	O
ATOM	2110	N	CYS	221	43.285	15.334	75.058	1.00	30.27	AAAA	N
ATOM	2112	CA	CYS	221	42.753	16.382	75.875	1.00	35.55	AAAA	C
ATOM	2113	C	CYS	221	41.460	17.055	75.452	1.00	47.06	AAAA	C
ATOM	2114	O	CYS	221	41.265	17.598	74.368	1.00	49.57	AAAA	O
ATOM	2115	CB	CYS	221	43.804	17.478	76.063	1.00	47.45	AAAA	C
ATOM	2116	SG	CYS	221	45.494	16.935	76.538	1.00	47.06	AAAA	S
ATOM	2117	N	ARG	222	40.503	17.133	76.396	1.00	51.47	AAAA	N
ATOM	2119	CA	ARG	222	39.281	17.906	76.338	1.00	51.86	AAAA	C
ATOM	2120	CB	ARG	222	38.647	18.074	77.712	1.00	54.53	AAAA	C
ATOM	2121	CG	ARG	222	37.314	18.687	77.854	1.00	45.56	AAAA	C
ATOM	2122	CD	ARG	222	36.538	18.338	79.087	1.00	54.45	AAAA	C
ATOM	2123	NE	ARG	222	36.272	16.947	79.269	1.00	65.53	AAAA	N
ATOM	2125	CZ	ARG	222	35.534	16.080	78.617	1.00	67.60	AAAA	C
ATOM	2126	NH1	ARG	222	34.925	16.599	77.533	1.00	70.26	AAAA	N
ATOM	2129	NH2	ARG	222	35.342	14.780	78.901	1.00	54.11	AAAA	N
ATOM	2132	C	ARG	222	39.562	19.286	75.740	1.00	50.66	AAAA	C
ATOM	2133	O	ARG	222	38.737	19.845	75.009	1.00	58.34	AAAA	O
ATOM	2134	N	HIS	223	40.556	19.981	76.190	1.00	45.65	AAAA	N
ATOM	2136	CA	HIS	223	40.998	21.291	75.921	1.00	46.93	AAAA	C
ATOM	2137	CB	HIS	223	41.067	22.251	77.011	1.00	49.51	AAAA	C
ATOM	2138	CG	HIS	223	39.710	22.344	77.617	1.00	58.83	AAAA	C
ATOM	2139	CD2	HIS	223	38.820	23.360	77.556	1.00	61.08	AAAA	C
ATOM	2140	ND1	HIS	223	39.082	21.388	78.425	1.00	63.28	AAAA	N
ATOM	2142	CE1	HIS	223	37.881	21.815	78.759	1.00	58.01	AAAA	C
ATOM	2143	NE2	HIS	223	37.681	23.010	78.232	1.00	48.56	AAAA	N
ATOM	2145	C	HIS	223	42.363	21.260	75.122	1.00	50.78	AAAA	C
ATOM	2146	O	HIS	223	42.506	20.753	74.003	1.00	47.43	AAAA	O
ATOM	2147	N	TYR	224	43.359	21.847	75.769	1.00	49.20	AAAA	N
ATOM	2149	CA	TYR	224	44.712	21.992	75.259	1.00	48.17	AAAA	C
ATOM	2150	CB	TYR	224	45.144	23.430	75.426	1.00	44.07	AAAA	C
ATOM	2151	CG	TYR	224	44.318	24.234	74.417	1.00	51.77	AAAA	C
ATOM	2152	CD1	TYR	224	43.193	24.869	74.904	1.00	48.94	AAAA	C
ATOM	2153	CE1	TYR	224	42.401	25.633	74.089	1.00	48.41	AAAA	C
ATOM	2154	CD2	TYR	224	44.623	24.358	73.065	1.00	54.82	AAAA	C
ATOM	2155	CE2	TYR	224	43.847	25.131	72.233	1.00	56.09	AAAA	C
ATOM	2156	CZ	TYR	224	42.739	25.745	72.766	1.00	54.23	AAAA	C
ATOM	2157	OH	TYR	224	41.915	26.522	72.017	1.00	61.70	AAAA	O
ATOM	2159	C	TYR	224	45.725	21.095	75.892	1.00	48.19	AAAA	C
ATOM	2160	O	TYR	224	45.776	20.913	77.111	1.00	55.75	AAAA	O
ATOM	2161	N	TYR	225	46.584	20.514	75.077	1.00	48.79	AAAA	N
ATOM	2163	CA	TYR	225	47.655	19.653	75.555	1.00	43.02	AAAA	C
ATOM	2164	CB	TYR	225	48.020	18.639	74.548	1.00	42.32	AAAA	C
ATOM	2165	CG	TYR	225	49.286	17.926	74.954	1.00	46.95	AAAA	C
ATOM	2166	CD1	TYR	225	49.299	16.858	75.817	1.00	43.57	AAAA	C
ATOM	2167	CE1	TYR	225	50.450	16.221	76.173	1.00	47.26	AAAA	C
ATOM	2168	CD2	TYR	225	50.487	18.407	74.401	1.00	52.82	AAAA	C
ATOM	2169	CE2	TYR	225	51.656	17.791	74.781	1.00	53.94	AAAA	C
ATOM	2170	CZ	TYR	225	51.639	16.707	75.644	1.00	52.31	AAAA	C
ATOM	2171	OH	TYR	225	52.806	16.186	75.905	1.00	50.71	AAAA	O
ATOM	2173	C	TYR	225	48.972	20.507	75.793	1.00	47.13	AAAA	C
ATOM	2174	O	TYR	225	49.080	21.514	75.150	1.00	53.97	AAAA	O
ATOM	2175	N	TYR	226	49.634	20.253	76.821	1.00	56.84	AAAA	N

ATOM	2177	CA	TYR	226	50.811	21.601	79.172	1.00	56.83	AAAA	C
ATOM	2178	CB	TYR	226	50.455	22.343	77.785	1.00	59.51	AAAA	C
ATOM	2179	CG	TYR	226	51.741	23.126	77.941	1.00	65.45	AAAA	C
ATOM	2180	CD1	TYR	226	52.121	23.557	79.197	1.00	69.12	AAAA	C
ATOM	2181	CE1	TYR	226	53.289	24.275	79.400	1.00	70.77	AAAA	C
ATOM	2182	CD2	TYR	226	52.580	23.409	76.864	1.00	69.38	AAAA	C
ATOM	2183	CE2	TYR	226	53.758	24.118	77.020	1.00	70.94	AAAA	C
ATOM	2184	CZ	TYR	226	54.099	24.549	78.301	1.00	72.96	AAAA	C
ATOM	2185	OH	TYR	226	55.267	25.254	78.435	1.00	70.84	AAAA	O
ATOM	2187	C	TYR	226	51.784	20.356	78.165	1.00	57.55	AAAA	C
ATOM	2188	O	TYR	226	51.492	20.133	79.350	1.00	56.90	AAAA	O
ATOM	2189	N	ALA	227	52.978	20.080	77.642	1.00	53.82	AAAA	N
ATOM	2191	CA	ALA	227	54.061	19.557	78.440	1.00	51.82	AAAA	C
ATOM	2192	CB	ALA	227	54.528	20.620	79.428	1.00	55.81	AAAA	C
ATOM	2193	C	ALA	227	53.600	18.309	79.170	1.00	53.56	AAAA	C
ATOM	2194	O	ALA	227	53.663	18.218	80.413	1.00	49.63	AAAA	O
ATOM	2195	N	GLY	228	53.076	17.360	78.393	1.00	50.68	AAAA	N
ATOM	2197	CA	GLY	228	52.585	16.135	79.028	1.00	49.02	AAAA	C
ATOM	2198	C	GLY	228	51.312	16.330	79.861	1.00	51.61	AAAA	C
ATOM	2199	O	GLY	228	51.028	15.538	80.776	1.00	51.10	AAAA	O
ATOM	2200	N	VAL	229	50.643	17.495	79.791	1.00	47.09	AAAA	N
ATOM	2202	CA	VAL	229	49.489	17.671	80.635	1.00	51.11	AAAA	C
ATOM	2203	CB	VAL	229	49.908	18.610	81.774	1.00	56.52	AAAA	C
ATOM	2204	CG1	VAL	229	48.627	18.896	82.566	1.00	38.39	AAAA	C
ATOM	2205	CG2	VAL	229	51.002	18.035	82.682	1.00	50.16	AAAA	C
ATOM	2206	C	VAL	229	48.255	18.173	79.873	1.00	51.37	AAAA	C
ATOM	2207	O	VAL	229	48.344	19.279	79.309	1.00	53.71	AAAA	O
ATOM	2208	N	CYS	230	47.100	17.518	80.036	1.00	42.21	AAAA	N
ATOM	2210	CA	CYS	230	45.881	18.117	79.471	1.00	40.32	AAAA	C
ATOM	2211	C	CYS	230	45.456	19.350	80.229	1.00	38.42	AAAA	C
ATOM	2212	O	CYS	230	44.964	19.248	81.321	1.00	41.62	AAAA	O
ATOM	2213	CB	CYS	230	44.746	17.132	79.370	1.00	31.54	AAAA	C
ATOM	2214	SG	CYS	230	45.149	15.753	78.266	1.00	43.61	AAAA	S
ATOM	2215	N	VAL	231	45.637	20.534	79.731	1.00	39.83	AAAA	N
ATOM	2217	CA	VAL	231	45.445	21.769	80.462	1.00	46.57	AAAA	C
ATOM	2218	CB	VAL	231	46.518	22.736	80.088	1.00	50.99	AAAA	C
ATOM	2219	CG1	VAL	231	46.798	23.878	81.053	1.00	50.41	AAAA	C
ATOM	2220	CG2	VAL	231	47.838	21.913	80.506	1.00	44.95	AAAA	C
ATOM	2221	C	VAL	231	44.111	22.321	80.057	1.00	52.59	AAAA	C
ATOM	2222	O	VAL	231	43.599	22.183	78.936	1.00	55.30	AAAA	O
ATOM	2223	N	PRO	232	43.482	23.105	80.913	1.00	54.28	AAAA	N
ATOM	2224	CD	PRO	232	43.830	23.385	82.320	1.00	54.25	AAAA	C
ATOM	2225	CA	PRO	232	42.153	23.625	80.575	1.00	54.39	AAAA	C
ATOM	2226	CB	PRO	232	41.537	23.877	81.928	1.00	53.73	AAAA	C
ATOM	2227	CG	PRO	232	42.683	24.287	82.765	1.00	55.00	AAAA	C
ATOM	2228	C	PRO	232	42.361	24.913	79.795	1.00	56.37	AAAA	C
ATOM	2229	O	PRO	232	41.498	25.482	79.137	1.00	55.79	AAAA	O
ATOM	2230	N	ALA	233	43.615	25.400	79.901	1.00	54.76	AAAA	N
ATOM	2232	CA	ALA	233	43.998	26.569	79.124	1.00	49.93	AAAA	C
ATOM	2233	CB	ALA	233	43.440	27.807	79.746	1.00	35.43	AAAA	C
ATOM	2234	C	ALA	233	45.502	26.662	78.974	1.00	49.79	AAAA	C
ATOM	2235	O	ALA	233	46.195	25.879	79.616	1.00	51.41	AAAA	O
ATOM	2236	N	CYS	234	45.984	27.508	78.072	1.00	45.07	AAAA	N
ATOM	2238	CA	CYS	234	47.430	27.518	77.907	1.00	48.63	AAAA	C
ATOM	2239	C	CYS	234	48.001	28.340	79.076	1.00	50.93	AAAA	C
ATOM	2240	O	CYS	234	47.650	29.513	79.250	1.00	47.57	AAAA	O
ATOM	2241	CB	CYS	234	47.816	28.034	76.511	1.00	43.10	AAAA	C
ATOM	2242	SG	CYS	234	47.608	26.789	75.226	1.00	43.04	AAAA	S
ATOM	2243	N	PRO	235	49.127	27.853	79.599	1.00	49.55	AAAA	N
ATOM	2244	CD	PRO	235	49.692	26.557	79.207	1.00	48.75	AAAA	C
ATOM	2245	CA	PRO	235	49.911	28.569	80.599	1.00	51.69	AAAA	C
ATOM	2246	CB	PRO	235	50.984	27.581	80.975	1.00	50.80	AAAA	C
ATOM	2247	CG	PRO	235	50.912	26.417	80.077	1.00	50.06	AAAA	C
ATOM	2248	C	PRO	235	50.487	29.852	80.050	1.00	57.11	AAAA	C
ATOM	2249	O	PRO	235	50.848	29.957	78.870	1.00	59.60	AAAA	O
ATOM	2250	N	PRO	236	50.676	30.875	80.887	1.00	59.85	AAAA	N
ATOM	2251	CD	PRO	236	50.405	30.822	82.363	1.00	55.85	AAAA	C
ATOM	2252	CA	PRO	236	51.323	32.143	80.493	1.00	52.27	AAAA	C
ATOM	2253	CB	PRO	236	51.695	32.814	81.826	1.00	53.62	AAAA	C
ATOM	2254	CG	PRO	236	50.652	32.277	82.751	1.00	56.73	AAAA	C
ATOM	2255	C	PRO	236	52.545	31.886	79.671	1.00	44.21	AAAA	C
ATOM	2256	O	PRO	236	53.219	30.892	79.929	1.00	43.40	AAAA	O
ATOM	2257	N	ASN	237	52.837	32.757	78.716	1.00	46.54	AAAA	N
ATOM	2259	CA	ASN	237	53.895	32.623	77.716	1.00	45.94	AAAA	C
ATOM	2260	CB	ASN	237	55.259	32.653	78.456	1.00	58.65	AAAA	C
ATOM	2261	CG	ASN	237	55.357	33.855	79.371	1.00	58.51	AAAA	C
ATOM	2262	OD1	ASN	237	56.044	33.783	80.379	1.00	72.25	AAAA	O
ATOM	2263	ND2	ASN	237	54.631	34.910	79.051	1.00	62.99	AAAA	N
ATOM	2266	C	ASN	237	53.897	31.425	76.788	1.00	46.87	AAAA	C
ATOM	2267	O	ASN	237	54.962	30.935	76.326	1.00	54.50	AAAA	O
ATOM	2268	N	THR	238	52.817	30.657	76.692	1.00	42.91	AAAA	N
ATOM	2270	CA	THR	238	52.617	29.567	75.780	1.00	40.20	AAAA	C
ATOM	2271	CB	THR	238	52.481	28.248	76.466	1.00	42.62	AAAA	C
ATOM	2272	OG1	THR	238	51.227	28.343	77.237	1.00	50.88	AAAA	O
ATOM	2274	CG2	THR	238	53.552	27.986	77.424	1.00	34.84	AAAA	C

ATOM	2275	C	THR	238	51.279	29.875	75.008	1.00	42.52	AAAA	C
ATOM	2276	O	THR	238	50.669	30.864	75.509	1.00	42.51	AAAA	O
ATOM	2277	II	TYR	239	51.051	29.488	73.832	1.00	42.62	AAAA	II
ATOM	2279	CA	TYR	239	49.949	29.959	73.024	1.00	41.97	AAAA	C
ATOM	2280	CB	TYR	239	50.457	30.907	71.931	1.00	44.86	AAAA	C
ATOM	2281	CG	TYR	239	51.099	32.125	72.564	1.00	42.05	AAAA	C
ATOM	2282	CD1	TYR	239	52.467	32.086	72.815	1.00	39.41	AAAA	C
ATOM	2283	CE1	TYR	239	53.092	33.152	73.415	1.00	43.27	AAAA	C
ATOM	2284	CD2	TYR	239	50.376	33.230	72.923	1.00	44.15	AAAA	C
ATOM	2285	CE2	TYR	239	50.972	34.310	73.536	1.00	46.22	AAAA	C
ATOM	2286	CC	TYR	239	52.339	34.243	73.779	1.00	50.42	AAAA	C
ATOM	2287	OH	TYR	239	53.013	35.289	74.387	1.00	55.47	AAAA	O
ATOM	2289	C	TYR	239	49.232	28.813	72.315	1.00	45.54	AAAA	C
ATOM	2290	O	TYR	239	49.920	27.810	72.021	1.00	46.66	AAAA	O
ATOM	2291	II	ARG	240	47.895	28.990	72.126	1.00	40.62	AAAA	II
ATOM	2293	CA	ARG	240	47.177	27.892	71.426	1.00	38.78	AAAA	C
ATOM	2294	CB	ARG	240	45.675	28.127	71.452	1.00	39.77	AAAA	C
ATOM	2295	CG	ARG	240	45.116	28.944	72.588	1.00	43.37	AAAA	C
ATOM	2296	CD	ARG	240	43.573	28.957	72.683	1.00	38.60	AAAA	C
ATOM	2297	IIE	ARG	240	43.114	29.683	71.455	1.00	53.95	AAAA	II
ATOM	2299	CC	ARG	240	43.123	31.015	71.530	1.00	48.07	AAAA	C
ATOM	2300	NH1	ARG	240	43.513	31.562	72.668	1.00	47.65	AAAA	N
ATOM	2303	NH2	ARG	240	42.788	31.778	70.533	1.00	51.03	AAAA	II
ATOM	2306	C	ARG	240	47.627	27.737	69.979	1.00	31.72	AAAA	C
ATOM	2307	O	ARG	240	47.937	28.730	69.302	1.00	32.37	AAAA	O
ATOM	2308	II	PHE	241	47.779	26.562	69.549	1.00	27.95	AAAA	II
ATOM	2310	CA	PHE	241	48.182	26.269	68.183	1.00	30.41	AAAA	C
ATOM	2311	CB	PHE	241	49.678	25.940	68.151	1.00	34.83	AAAA	C
ATOM	2312	CG	PHE	241	50.235	25.653	66.773	1.00	26.84	AAAA	C
ATOM	2313	CD1	PHE	241	50.165	26.567	65.753	1.00	25.31	AAAA	C
ATOM	2314	CD2	PHE	241	50.785	24.417	66.573	1.00	27.38	AAAA	C
ATOM	2315	CE1	PHE	241	50.676	26.232	64.509	1.00	37.24	AAAA	C
ATOM	2316	CE2	PHE	241	51.294	24.101	65.320	1.00	38.45	AAAA	C
ATOM	2317	CC	PHE	241	51.281	25.010	64.281	1.00	21.17	AAAA	C
ATOM	2318	C	PHE	241	47.382	25.089	67.621	1.00	35.77	AAAA	C
ATOM	2319	O	PHE	241	47.543	24.013	68.186	1.00	36.77	AAAA	O
ATOM	2320	II	GLU	242	46.738	25.301	66.468	1.00	32.30	AAAA	II
ATOM	2322	CA	GLU	242	45.964	24.269	65.805	1.00	35.43	AAAA	C
ATOM	2323	CB	GLU	242	46.953	23.144	65.472	1.00	37.98	AAAA	C
ATOM	2324	CG	GLU	242	47.867	23.415	64.314	1.00	38.63	AAAA	C
ATOM	2325	CD	GLU	242	47.207	23.965	63.075	1.00	39.27	AAAA	C
ATOM	2326	OE1	GLU	242	46.380	23.205	62.517	1.00	42.79	AAAA	O
ATOM	2327	OE2	GLU	242	47.354	25.109	62.626	1.00	36.36	AAAA	O
ATOM	2328	C	GLU	242	44.752	23.771	66.600	1.00	34.36	AAAA	C
ATOM	2329	O	GLU	242	44.390	22.611	66.511	1.00	28.53	AAAA	O
ATOM	2330	II	GLY	243	44.135	24.589	67.449	1.00	36.94	AAAA	II
ATOM	2332	CA	GLY	243	43.048	24.154	68.303	1.00	34.57	AAAA	C
ATOM	2333	C	GLY	243	43.428	23.107	69.319	1.00	37.76	AAAA	C
ATOM	2334	O	GLY	243	42.474	22.473	69.746	1.00	43.00	AAAA	O
ATOM	2335	II	TRP	244	44.637	22.636	69.611	1.00	39.53	AAAA	II
ATOM	2337	CA	TRP	244	44.797	21.536	70.566	1.00	40.85	AAAA	C
ATOM	2338	CB	TRP	244	44.774	20.271	69.764	1.00	26.76	AAAA	C
ATOM	2339	CG	TRP	244	46.012	19.885	69.029	1.00	43.19	AAAA	C
ATOM	2340	CD2	TRP	244	47.019	18.983	69.498	1.00	39.55	AAAA	C
ATOM	2341	CE2	TRP	244	47.998	19.906	68.489	1.00	36.50	AAAA	C
ATOM	2342	CE3	TRP	244	47.186	18.254	70.692	1.00	32.18	AAAA	C
ATOM	2343	CD1	TRP	244	46.424	20.308	67.779	1.00	43.37	AAAA	C
ATOM	2344	IIE1	TRP	244	47.595	19.727	67.469	1.00	38.89	AAAA	II
ATOM	2346	CC2	TRP	244	49.150	18.128	68.620	1.00	39.01	AAAA	C
ATOM	2347	CC3	TRP	244	48.336	17.478	70.815	1.00	43.98	AAAA	C
ATOM	2348	CH2	TRP	244	49.322	17.425	69.784	1.00	42.50	AAAA	C
ATOM	2349	C	TRP	244	45.998	21.517	71.509	1.00	42.98	AAAA	C
ATOM	2350	O	TRP	244	46.253	20.501	72.146	1.00	42.70	AAAA	O
ATOM	2351	II	ARG	245	46.888	22.485	71.435	1.00	44.16	AAAA	II
ATOM	2353	CA	ARG	245	48.168	22.472	72.095	1.00	46.47	AAAA	C
ATOM	2354	CB	ARG	245	49.203	21.602	71.367	1.00	47.30	AAAA	C
ATOM	2355	CG	ARG	245	49.985	22.203	70.203	1.00	48.97	AAAA	C
ATOM	2356	CD	ARG	245	51.129	21.552	69.819	1.00	39.28	AAAA	C
ATOM	2357	IIE	ARG	245	51.586	21.665	68.444	1.00	50.86	AAAA	II
ATOM	2359	CC	ARG	245	52.629	21.044	67.895	1.00	46.73	AAAA	C
ATOM	2360	IIH1	ARG	245	53.344	20.236	68.653	1.00	50.15	AAAA	II
ATOM	2363	IIH2	ARG	245	53.072	21.126	66.638	1.00	41.69	AAAA	II
ATOM	2366	C	ARG	245	48.771	23.863	72.271	1.00	46.01	AAAA	C
ATOM	2367	O	ARG	245	48.394	24.793	71.541	1.00	47.44	AAAA	O
ATOM	2368	II	CYS	246	49.625	23.881	73.317	1.00	42.08	AAAA	II
ATOM	2370	CA	CYS	246	50.246	25.199	73.628	1.00	43.48	AAAA	C
ATOM	2371	C	CYS	246	51.695	25.217	73.183	1.00	43.38	AAAA	C
ATOM	2372	O	CYS	246	52.476	24.239	73.320	1.00	42.51	AAAA	O
ATOM	2373	CB	CYS	246	50.102	25.392	75.138	1.00	48.91	AAAA	C
ATOM	2374	SG	CYS	246	48.386	25.049	75.797	1.00	43.68	AAAA	S
ATOM	2375	II	VAL	247	52.101	26.288	72.564	1.00	41.21	AAAA	II
ATOM	2377	CA	VAL	247	53.417	26.468	71.982	1.00	36.51	AAAA	C
ATOM	2378	CB	VAL	247	53.569	26.357	70.444	1.00	36.87	AAAA	C
ATOM	2379	CG1	VAL	247	53.089	24.988	70.024	1.00	32.71	AAAA	C
ATOM	2380	CG2	VAL	247	53.129	27.602	69.729	1.00	28.20	AAAA	C

ATOM	2381	C	VAL	247	53.969	27.812	72.375	1.00	39.37	AAAA	C
ATOM	2382	O	VAL	247	53.230	28.770	72.549	1.00	38.80	AAAA	O
ATOM	2383	N	ASP	248	55.291	27.820	72.711	1.00	45.21	AAAA	N
ATOM	2385	CA	ASP	248	55.895	29.115	73.098	1.00	40.19	AAAA	C
ATOM	2386	CB	ASP	248	57.091	28.946	73.953	1.00	42.63	AAAA	C
ATOM	2387	CG	ASP	248	58.126	27.997	73.394	1.00	59.81	AAAA	C
ATOM	2388	OD1	ASP	248	59.067	27.795	74.187	1.00	53.06	AAAA	O
ATOM	2389	OD2	ASP	248	58.167	27.395	72.313	1.00	69.51	AAAA	O
ATOM	2390	C	ASP	248	56.315	29.883	71.839	1.00	36.99	AAAA	C
ATOM	2391	O	ASP	248	56.292	29.288	70.772	1.00	39.70	AAAA	O
ATOM	2392	N	ARG	249	56.545	31.163	71.918	1.00	30.72	AAAA	N
ATOM	2394	CA	ARG	249	56.950	32.057	70.906	1.00	36.17	AAAA	C
ATOM	2395	CB	ARG	249	57.223	33.495	71.491	1.00	21.29	AAAA	C
ATOM	2396	CG	ARG	249	57.594	34.424	70.326	1.00	24.96	AAAA	C
ATOM	2397	CD	ARG	249	57.814	35.811	70.843	1.00	21.23	AAAA	C
ATOM	2398	NE	ARG	249	56.658	36.150	71.689	1.00	39.75	AAAA	N
ATOM	2400	CZ	ARG	249	55.632	36.823	71.101	1.00	39.35	AAAA	C
ATOM	2401	NH1	ARG	249	55.642	37.118	69.801	1.00	25.41	AAAA	N
ATOM	2404	NH2	ARG	249	54.641	37.118	71.946	1.00	44.04	AAAA	N
ATOM	2407	C	ARG	249	58.134	31.685	70.010	1.00	40.63	AAAA	C
ATOM	2408	O	ARG	249	58.086	31.923	68.797	1.00	44.79	AAAA	O
ATOM	2409	N	ASP	250	59.149	30.974	70.468	1.00	41.87	AAAA	N
ATOM	2411	CA	ASP	250	60.287	30.739	69.606	1.00	46.90	AAAA	C
ATOM	2412	CB	ASP	250	61.740	30.726	70.154	1.00	53.11	AAAA	C
ATOM	2413	CG	ASP	250	62.421	32.122	70.081	1.00	71.49	AAAA	C
ATOM	2414	OD1	ASP	250	63.124	32.682	69.176	1.00	58.53	AAAA	O
ATOM	2415	OD2	ASP	250	62.272	32.928	71.071	1.00	70.30	AAAA	O
ATOM	2416	C	ASP	250	59.881	29.536	68.771	1.00	41.22	AAAA	O
ATOM	2417	O	ASP	250	60.291	29.443	67.616	1.00	39.06	AAAA	O
ATOM	2418	N	PHE	251	59.116	28.609	69.299	1.00	36.13	AAAA	N
ATOM	2420	CA	PHE	251	58.457	27.601	68.489	1.00	34.88	AAAA	C
ATOM	2421	CB	PHE	251	57.468	26.746	69.256	1.00	29.82	AAAA	C
ATOM	2422	CG	PHE	251	56.701	25.801	68.385	1.00	41.59	AAAA	C
ATOM	2423	CD1	PHE	251	57.101	24.479	68.263	1.00	30.66	AAAA	C
ATOM	2424	CD2	PHE	251	55.559	26.213	67.686	1.00	37.78	AAAA	C
ATOM	2425	CE1	PHE	251	56.414	23.557	67.424	1.00	29.30	AAAA	C
ATOM	2426	CE2	PHE	251	54.847	25.372	66.856	1.00	36.09	AAAA	C
ATOM	2427	CZ	PHE	251	55.294	24.070	66.715	1.00	36.21	AAAA	C
ATOM	2428	C	PHE	251	57.624	28.290	67.338	1.00	39.28	AAAA	C
ATOM	2429	O	PHE	251	57.811	28.010	66.144	1.00	30.27	AAAA	O
ATOM	2430	N	CYS	252	56.734	29.225	67.713	1.00	35.13	AAAA	N
ATOM	2432	CA	CYS	252	55.895	29.870	66.728	1.00	38.80	AAAA	C
ATOM	2433	C	CYS	252	56.827	30.598	65.747	1.00	44.73	AAAA	C
ATOM	2434	O	CYS	252	56.552	30.534	64.536	1.00	43.20	AAAA	O
ATOM	2435	CB	CYS	252	54.903	30.778	67.379	1.00	35.65	AAAA	C
ATOM	2436	SG	CYS	252	53.562	31.544	66.459	1.00	39.03	AAAA	S
ATOM	2437	N	ALA	253	57.872	31.256	66.285	1.00	41.53	AAAA	N
ATOM	2439	CA	ALA	253	58.687	32.071	65.415	1.00	40.39	AAAA	C
ATOM	2440	CB	ALA	253	59.529	33.089	66.172	1.00	36.07	AAAA	C
ATOM	2441	C	ALA	253	59.551	31.167	64.539	1.00	42.88	AAAA	C
ATOM	2442	O	ALA	253	60.147	31.735	63.640	1.00	47.42	AAAA	O
ATOM	2443	N	ASN	254	59.657	29.859	64.700	1.00	38.75	AAAA	N
ATOM	2445	CA	ASN	254	60.546	29.073	63.929	1.00	42.94	AAAA	C
ATOM	2446	CB	ASN	254	61.667	28.497	64.847	1.00	48.09	AAAA	C
ATOM	2447	CG	ASN	254	62.696	29.635	65.031	1.00	49.54	AAAA	C
ATOM	2448	OD1	ASN	254	63.468	29.840	64.081	1.00	61.38	AAAA	O
ATOM	2449	ND2	ASN	254	62.607	30.321	66.144	1.00	48.38	AAAA	N
ATOM	2452	C	ASN	254	59.907	27.959	63.135	1.00	53.72	AAAA	C
ATOM	2453	O	ASN	254	60.552	26.965	62.804	1.00	51.19	AAAA	O
ATOM	2454	N	ILE	255	58.612	28.136	62.766	1.00	57.77	AAAA	N
ATOM	2456	CA	ILE	255	57.828	27.107	62.134	1.00	53.28	AAAA	C
ATOM	2457	CB	ILE	255	56.329	27.322	62.304	1.00	50.41	AAAA	C
ATOM	2458	CG2	ILE	255	55.477	26.595	61.246	1.00	51.95	AAAA	C
ATOM	2459	CG1	ILE	255	55.778	26.675	63.553	1.00	40.59	AAAA	C
ATOM	2460	CD1	ILE	255	54.479	27.317	64.006	1.00	38.97	AAAA	C
ATOM	2461	C	ILE	255	58.127	26.886	60.651	1.00	52.62	AAAA	C
ATOM	2462	O	ILE	255	58.196	25.709	60.252	1.00	53.96	AAAA	O
ATOM	2463	N	LEU	256	58.290	27.960	59.918	1.00	49.96	AAAA	N
ATOM	2465	CA	LEU	256	58.680	27.764	58.516	1.00	63.68	AAAA	C
ATOM	2466	CB	LEU	256	58.175	29.012	57.799	1.00	56.80	AAAA	C
ATOM	2467	CG	LEU	256	56.671	29.196	57.864	1.00	59.11	AAAA	C
ATOM	2468	CD1	LEU	256	56.310	30.654	57.645	1.00	43.31	AAAA	C
ATOM	2469	CD2	LEU	256	55.965	28.222	56.928	1.00	55.88	AAAA	C
ATOM	2470	C	LEU	256	60.193	27.622	58.355	1.00	66.23	AAAA	C
ATOM	2471	O	LEU	256	60.691	27.511	57.249	1.00	70.29	AAAA	O
ATOM	2472	N	SER	257	60.942	27.559	59.430	1.00	64.61	AAAA	N
ATOM	2474	CA	SER	257	62.352	27.529	59.534	1.00	69.23	AAAA	C
ATOM	2475	CB	SER	257	62.924	27.318	60.955	1.00	62.45	AAAA	C
ATOM	2476	OG	SER	257	63.381	25.980	61.074	1.00	56.18	AAAA	O
ATOM	2478	C	SER	257	62.973	26.497	58.610	1.00	70.77	AAAA	C
ATOM	2479	O	SER	257	64.122	26.731	59.245	1.00	72.50	AAAA	O
ATOM	2480	N	ALA	258	62.322	25.399	58.329	1.00	74.61	AAAA	N
ATOM	2482	CA	ALA	258	62.933	24.488	57.313	1.00	76.34	AAAA	C
ATOM	2483	CB	ALA	258	62.570	23.039	57.584	1.00	80.82	AAAA	C
ATOM	2484	C	ALA	258	62.663	24.964	55.921	1.00	78.21	AAAA	C

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ATOM   2485   O    ALA   258   62.980   24.139   55.020   1.00  79.60   AAAA  O
ATOM   2486   N    GLU   259   62.069   26.109   55.651   1.00  79.05   AAAA  N
ATOM   2488   CA   GLU   259   61.740   26.621   54.349   1.00  83.84   AAAA  C
ATOM   2489   CB   GLU   259   60.225   26.457   54.135   1.00  86.99   AAAA  C
ATOM   2490   CG   GLU   259   59.687   25.049   54.314   1.00  99.38   AAAA  C
ATOM   2491   CD   GLU   259   58.364   25.032   55.057   1.00  97.77   AAAA  C
ATOM   2492   OE1  GLU   259   58.080   24.088   55.838   1.00 101.45   AAAA  O
ATOM   2493   OE2  GLU   259   57.598   26.002   54.837   1.00  94.58   AAAA  O
ATOM   2494   C    GLU   259   62.117   28.078   54.083   1.00  85.43   AAAA  C
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ATOM   2549   CD1  PHE   266   53.760   30.618   60.377   1.00  34.72   AAAA  C
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ATOM   2591  OD1 ASP  270   41.737  38.379  69.835  1.00 90.92      AAAA O
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ATOM   2598  C   GLY  271   46.819  32.998  71.537  1.00 39.15      AAAA C
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ATOM   2622  SD  MET  274   45.477  33.921  64.677  1.00 40.00      AAAA S
ATOM   2623  CE  MET  274   45.659  35.658  64.754  1.00 22.47      AAAA C
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ATOM	2742	OE1	GLN	287	58.192	37.023	57.845	1.00	28.18	AAAA	O
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ATOM	2755	O	SER	288	54.993	39.776	62.553	1.00	31.16	AAAA	O
ATOM	2756	N	MET	289	55.774	39.720	64.621	1.00	32.51	AAAA	N
ATOM	2758	CA	MET	289	54.975	38.697	65.105	1.00	34.53	AAAA	C
ATOM	2759	CB	MET	289	55.507	37.823	66.153	1.00	30.31	AAAA	C
ATOM	2760	CG	MET	289	56.571	36.872	65.680	1.00	40.50	AAAA	C
ATOM	2761	SD	MET	289	56.977	35.623	66.881	1.00	31.65	AAAA	S
ATOM	2762	CE	MET	289	55.745	34.315	66.508	1.00	30.47	AAAA	C
ATOM	2763	C	MET	289	53.557	39.286	65.703	1.00	35.55	AAAA	C
ATOM	2764	O	MET	289	52.630	38.512	66.014	1.00	38.37	AAAA	O
ATOM	2765	N	TYR	290	53.380	40.565	65.742	1.00	29.54	AAAA	N
ATOM	2767	CA	TYR	290	52.363	41.358	66.297	1.00	38.81	AAAA	C
ATOM	2768	CB	TYR	290	52.947	42.589	67.042	1.00	36.72	AAAA	C
ATOM	2769	CG	TYR	290	53.570	42.184	68.351	1.00	41.94	AAAA	C
ATOM	2770	CD1	TYR	290	54.932	41.780	68.350	1.00	37.79	AAAA	C
ATOM	2771	CE1	TYR	290	55.548	41.368	69.503	1.00	32.60	AAAA	C
ATOM	2772	CD2	TYR	290	52.887	42.157	69.570	1.00	39.93	AAAA	C
ATOM	2773	CE2	TYR	290	53.501	41.750	70.748	1.00	36.16	AAAA	C
ATOM	2774	CZ	TYR	290	54.922	41.355	70.693	1.00	38.85	AAAA	C
ATOM	2775	OH	TYR	290	55.581	40.923	71.751	1.00	43.41	AAAA	O
ATOM	2777	C	TYR	290	51.361	41.955	65.270	1.00	45.54	AAAA	C
ATOM	2778	O	TYR	290	51.733	42.520	64.227	1.00	47.10	AAAA	O
ATOM	2779	N	CYS	291	50.071	41.698	65.537	1.00	44.68	AAAA	N
ATOM	2781	CA	CYS	291	49.017	42.205	64.685	1.00	47.20	AAAA	C
ATOM	2782	C	CYS	291	48.295	43.434	65.194	1.00	46.06	AAAA	C
ATOM	2783	O	CYS	291	47.892	43.550	66.343	1.00	49.45	AAAA	O
ATOM	2784	CB	CYS	291	47.973	41.103	64.483	1.00	43.44	AAAA	C
ATOM	2785	SG	CYS	291	48.766	39.715	63.683	1.00	45.49	AAAA	S
ATOM	2786	N	ILE	292	48.136	44.453	64.365	1.00	46.82	AAAA	N
ATOM	2788	CA	ILE	292	47.399	45.651	64.755	1.00	50.64	AAAA	C
ATOM	2789	CB	ILE	292	48.267	46.932	64.779	1.00	39.19	AAAA	C
ATOM	2790	CG2	ILE	292	49.291	46.885	65.861	1.00	44.39	AAAA	C
ATOM	2791	CG1	ILE	292	48.920	47.095	63.402	1.00	44.29	AAAA	C

ATOM	2792	CD1	ILE	292	49.234	48.564	63.108	1.00	32.89	AAAA	C
ATOM	2793	C	ILE	292	46.240	46.003	63.806	1.00	50.01	AAAA	C
ATOM	2794	O	ILE	292	46.165	45.526	62.670	1.00	46.64	AAAA	O
ATOM	2795	N	PRO	293	45.150	46.507	64.385	1.00	51.86	AAAA	N
ATOM	2796	CD	PRO	293	45.009	46.804	65.839	1.00	51.05	AAAA	C
ATOM	2797	CA	PRO	293	43.958	46.930	63.675	1.00	51.40	AAAA	C
ATOM	2798	CB	PRO	293	43.170	47.784	64.681	1.00	49.00	AAAA	C
ATOM	2799	CG	PRO	293	43.533	47.112	65.951	1.00	53.73	AAAA	C
ATOM	2800	C	PRO	293	44.253	47.870	62.525	1.00	51.68	AAAA	C
ATOM	2801	O	PRO	293	45.053	48.788	62.737	1.00	51.92	AAAA	O
ATOM	2802	N	CYS	294	43.607	47.621	61.408	1.00	50.66	AAAA	N
ATOM	2804	CA	CYS	294	43.811	48.464	60.254	1.00	57.90	AAAA	C
ATOM	2805	C	CYS	294	43.219	49.848	60.345	1.00	59.59	AAAA	C
ATOM	2806	O	CYS	294	43.744	50.814	59.785	1.00	60.87	AAAA	O
ATOM	2807	CB	CYS	294	43.229	47.686	59.046	1.00	57.59	AAAA	C
ATOM	2808	SG	CYS	294	44.408	46.460	58.563	1.00	51.12	AAAA	S
ATOM	2809	N	ALA	295	42.009	50.031	60.854	1.00	65.87	AAAA	N
ATOM	2811	CA	ALA	295	41.391	51.386	60.804	1.00	71.19	AAAA	C
ATOM	2812	CB	ALA	295	42.311	52.459	61.393	1.00	63.82	AAAA	C
ATOM	2813	C	ALA	295	40.971	51.770	59.379	1.00	69.17	AAAA	C
ATOM	2814	O	ALA	295	41.421	52.717	58.762	1.00	64.70	AAAA	O
ATOM	2815	N	GLY	296	40.153	50.920	58.775	1.00	71.30	AAAA	N
ATOM	2817	CA	GLY	296	39.640	51.049	57.416	1.00	72.66	AAAA	C
ATOM	2818	C	GLY	296	39.895	49.686	56.769	1.00	74.20	AAAA	C
ATOM	2819	O	GLY	296	40.408	48.819	57.490	1.00	75.04	AAAA	O
ATOM	2820	N	PRO	297	39.561	49.540	55.497	1.00	71.98	AAAA	N
ATOM	2821	CD	PRO	297	38.928	50.561	54.637	1.00	72.15	AAAA	C
ATOM	2822	CA	PRO	297	39.958	48.344	54.777	1.00	68.23	AAAA	C
ATOM	2823	CB	PRO	297	39.488	48.603	53.369	1.00	72.57	AAAA	C
ATOM	2824	CG	PRO	297	38.470	49.687	53.490	1.00	74.01	AAAA	C
ATOM	2825	C	PRO	297	41.480	48.306	54.860	1.00	65.78	AAAA	C
ATOM	2826	O	PRO	297	42.147	49.323	54.997	1.00	62.72	AAAA	O
ATOM	2827	N	CYS	298	42.039	47.135	55.073	1.00	63.85	AAAA	N
ATOM	2829	CA	CYS	298	43.464	46.953	55.248	1.00	54.47	AAAA	C
ATOM	2830	C	CYS	298	44.109	47.303	53.908	1.00	54.56	AAAA	C
ATOM	2831	O	CYS	298	43.621	47.030	52.820	1.00	54.83	AAAA	O
ATOM	2832	CB	CYS	298	43.665	45.544	55.669	1.00	47.65	AAAA	C
ATOM	2833	SG	CYS	298	43.501	45.115	57.371	1.00	46.12	AAAA	S
ATOM	2834	N	PRO	299	45.310	47.876	53.967	1.00	49.83	AAAA	N
ATOM	2835	CD	PRO	299	46.087	48.168	55.194	1.00	48.14	AAAA	C
ATOM	2836	CA	PRO	299	46.055	48.212	52.787	1.00	43.67	AAAA	C
ATOM	2837	CB	PRO	299	47.267	48.965	53.281	1.00	44.08	AAAA	C
ATOM	2838	CG	PRO	299	47.454	48.361	54.628	1.00	51.38	AAAA	C
ATOM	2839	C	PRO	299	46.341	46.969	52.010	1.00	38.86	AAAA	C
ATOM	2840	O	PRO	299	46.372	45.874	52.546	1.00	42.85	AAAA	O
ATOM	2841	N	LYS	300	46.310	47.073	50.712	1.00	38.30	AAAA	N
ATOM	2843	CA	LYS	300	46.484	45.958	49.812	1.00	42.62	AAAA	C
ATOM	2844	CB	LYS	300	45.176	45.226	49.595	1.00	34.28	AAAA	C
ATOM	2845	CG	LYS	300	45.346	43.901	48.920	1.00	41.45	AAAA	C
ATOM	2846	CD	LYS	300	44.013	43.413	48.378	1.00	48.31	AAAA	C
ATOM	2847	CE	LYS	300	44.388	42.027	47.797	1.00	48.57	AAAA	C
ATOM	2848	NZ	LYS	300	43.662	42.031	46.478	1.00	63.70	AAAA	N
ATOM	2852	C	LYS	300	46.964	46.479	48.432	1.00	48.72	AAAA	C
ATOM	2853	O	LYS	300	46.413	47.383	47.776	1.00	46.09	AAAA	O
ATOM	2854	N	VAL	301	48.150	45.984	48.054	1.00	48.15	AAAA	N
ATOM	2856	CA	VAL	301	48.802	46.462	46.871	1.00	44.52	AAAA	C
ATOM	2857	CB	VAL	301	50.292	46.729	47.074	1.00	51.52	AAAA	C
ATOM	2858	CG1	VAL	301	51.008	47.200	45.796	1.00	43.07	AAAA	C
ATOM	2859	CG2	VAL	301	50.495	47.794	48.141	1.00	49.50	AAAA	C
ATOM	2860	C	VAL	301	48.516	45.410	45.837	1.00	44.59	AAAA	C
ATOM	2861	O	VAL	301	48.913	44.291	46.060	1.00	43.70	AAAA	O
ATOM	2862	N	CYS	302	47.910	45.816	44.718	1.00	47.98	AAAA	N
ATOM	2864	CA	CYS	302	47.645	44.735	43.739	1.00	55.19	AAAA	C
ATOM	2865	C	CYS	302	48.594	44.968	42.583	1.00	57.64	AAAA	C
ATOM	2866	O	CYS	302	48.852	46.152	42.313	1.00	60.23	AAAA	O
ATOM	2867	CB	CYS	302	46.186	44.630	43.330	1.00	68.30	AAAA	C
ATOM	2868	SG	CYS	302	45.070	44.360	44.751	1.00	70.31	AAAA	S
ATOM	2869	N	GLU	303	49.103	43.921	42.075	1.00	58.15	AAAA	N
ATOM	2871	CA	GLU	303	50.174	43.932	41.034	1.00	62.85	AAAA	N
ATOM	2872	CB	GLU	303	51.503	44.006	41.595	1.00	67.85	AAAA	C
ATOM	2873	CG	GLU	303	51.760	43.487	43.014	0.01	67.46	AAAA	C
ATOM	2874	CD	GLU	303	51.999	41.992	43.097	0.01	67.91	AAAA	C
ATOM	2875	OE1	GLU	303	53.011	41.514	42.561	0.01	67.67	AAAA	O
ATOM	2876	OE2	GLU	303	51.147	41.299	43.697	0.01	67.65	AAAA	O
ATOM	2877	C	GLU	303	50.096	42.662	40.194	1.00	64.12	AAAA	C
ATOM	2878	O	GLU	303	50.162	41.562	40.708	1.00	65.08	AAAA	O
ATOM	2879	N	GLU	304	49.967	42.794	38.904	1.00	67.37	AAAA	N
ATOM	2881	CA	GLU	304	49.672	41.583	38.094	1.00	74.63	AAAA	C
ATOM	2882	CB	GLU	304	48.285	41.596	37.458	1.00	71.71	AAAA	C
ATOM	2883	CG	GLU	304	47.339	42.663	38.031	1.00	84.54	AAAA	C
ATOM	2884	CD	GLU	304	45.930	42.152	36.185	1.00	87.56	AAAA	C
ATOM	2885	OE1	GLU	304	45.438	41.571	37.179	1.00	89.13	AAAA	O
ATOM	2886	OE2	GLU	304	45.249	42.269	39.233	1.00	93.19	AAAA	O
ATOM	2887	C	GLU	304	50.966	41.307	37.190	1.00	76.10	AAAA	C
ATOM	2888	O	GLU	304	51.911	41.962	37.217	1.00	74.78	AAAA	O

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ATOM   2989  N   GLU   305    50.899  40.126  36.566  1.00  77.31      AAAA N
ATOM   2991  CA  GLU   305    51.932  39.656  35.674  1.00  75.96      AAAA C
ATOM   2992  CB  GLU   305    51.467  38.380  34.979  1.00  79.85      AAAA C
ATOM   2993  CG  GLU   305    52.307  37.937  33.807  1.00  87.28      AAAA C
ATOM   2894  CD  GLU   305    51.758  36.891  32.886  0.01  83.39      AAAA C
ATOM   2895  OE1 GLU   305    50.762  36.234  33.252  0.01  83.66      AAAA O
ATOM   2896  OE2 GLU   305    52.310  36.700  31.780  0.01  83.73      AAAA O
ATOM   2997  C   GLU   305    52.276  40.737  34.666  1.00  75.97      AAAA C
ATOM   2998  O   GLU   305    53.381  41.268  34.613  1.00  76.54      AAAA O
ATOM   2999  N   LYS   306    51.291  41.181  33.882  1.00  78.22      AAAA N
ATOM   2900  CA  LYS   306    51.479  42.329  33.004  1.00  75.99      AAAA C
ATOM   2902  CB  LYS   306    50.467  42.253  31.855  1.00  79.78      AAAA C
ATOM   2903  CG  LYS   306    51.208  42.227  30.527  1.00  94.52      AAAA C
ATOM   2904  CD  LYS   306    50.313  42.191  29.314  1.00  92.78      AAAA C
ATOM   2905  CE  LYS   306    50.740  43.227  28.261  1.00  97.10      AAAA C
ATOM   2906  NZ  LYS   306    50.938  44.554  28.929  1.00  84.87      AAAA N
ATOM   2910  C   LYS   306    51.381  43.669  33.703  1.00  73.85      AAAA C
ATOM   2911  O   LYS   306    50.703  43.862  34.718  1.00  76.08      AAAA O
ATOM   2912  N   LYS   307    52.000  44.700  33.180  1.00  71.15      AAAA N
ATOM   2914  CA  LYS   307    51.934  46.053  33.692  1.00  69.45      AAAA C
ATOM   2915  CB  LYS   307    53.022  46.903  33.008  1.00  79.64      AAAA C
ATOM   2916  CG  LYS   307    54.419  46.837  33.564  1.00  78.88      AAAA C
ATOM   2917  CD  LYS   307    55.257  48.084  33.374  1.00  85.84      AAAA C
ATOM   2918  CE  LYS   307    55.708  48.215  31.924  1.00  97.07      AAAA C
ATOM   2919  NZ  LYS   307    54.649  48.840  31.067  1.00  97.80      AAAA N
ATOM   2923  C   LYS   307    50.562  46.716  33.525  1.00  67.97      AAAA C
ATOM   2924  O   LYS   307    50.010  47.369  34.431  1.00  64.46      AAAA O
ATOM   2925  N   THR   308    49.979  46.661  32.323  1.00  65.84      AAAA N
ATOM   2927  CA  THR   308    48.709  47.319  32.091  1.00  64.56      AAAA C
ATOM   2928  CB  THR   308    48.714  47.977  30.711  1.00  59.91      AAAA C
ATOM   2929  OG1 THR   308    49.834  48.843  30.577  1.00  61.97      AAAA O
ATOM   2931  CG2 THR   308    47.392  48.742  30.561  1.00  63.64      AAAA C
ATOM   2932  C   THR   308    47.514  46.379  32.234  1.00  61.82      AAAA C
ATOM   2933  O   THR   308    47.412  45.415  31.477  1.00  62.05      AAAA O
ATOM   2934  N   LYS   309    46.675  46.719  33.211  1.00  55.66      AAAA N
ATOM   2936  CA  LYS   309    45.456  45.926  33.445  1.00  54.67      AAAA C
ATOM   2937  CB  LYS   309    45.043  45.880  34.904  1.00  56.82      AAAA C
ATOM   2938  CG  LYS   309    43.601  45.541  35.223  1.00  57.50      AAAA C
ATOM   2939  CD  LYS   309    43.390  44.039  35.086  1.00  59.50      AAAA C
ATOM   2940  CE  LYS   309    42.703  43.448  36.324  1.00  57.31      AAAA C
ATOM   2941  NZ  LYS   309    42.758  41.954  36.236  1.00  57.22      AAAA N
ATOM   2945  C   LYS   309    44.391  46.570  32.548  1.00  51.21      AAAA C
ATOM   2946  O   LYS   309    44.074  47.763  32.680  1.00  47.23      AAAA O
ATOM   2947  N   THR   310    43.895  45.772  31.610  1.00  47.67      AAAA N
ATOM   2949  CA  THR   310    42.862  46.328  30.733  1.00  51.89      AAAA C
ATOM   2950  CB  THR   310    43.161  46.015  29.266  1.00  54.81      AAAA C
ATOM   2951  OG1 THR   310    41.909  45.710  28.635  1.00  66.20      AAAA O
ATOM   2953  CG2 THR   310    44.032  44.791  29.139  1.00  55.18      AAAA C
ATOM   2954  C   THR   310    41.468  45.841  31.117  1.00  51.15      AAAA C
ATOM   2955  O   THR   310    41.162  44.680  30.991  1.00  49.27      AAAA O
ATOM   2956  N   ILE   311    40.684  46.706  31.732  1.00  50.18      AAAA N
ATOM   2958  CA  ILE   311    39.363  46.453  32.278  1.00  48.67      AAAA C
ATOM   2959  CB  ILE   311    39.120  47.396  33.462  1.00  49.27      AAAA C
ATOM   2960  CG2 ILE   311    37.655  47.596  33.799  1.00  50.72      AAAA C
ATOM   2961  CG1 ILE   311    39.896  48.699  34.699  1.00  41.34      AAAA C
ATOM   2962  CD1 ILE   311    39.847  48.073  35.739  1.00  52.22      AAAA C
ATOM   2963  C   ILE   311    38.334  46.729  31.186  1.00  45.37      AAAA C
ATOM   2964  O   ILE   311    38.132  47.875  30.758  1.00  37.14      AAAA O
ATOM   2965  N   ASP   312    37.971  45.678  30.524  1.00  50.10      AAAA N
ATOM   2967  CA  ASP   312    36.991  45.842  29.377  1.00  56.35      AAAA C
ATOM   2968  CB  ASP   312    37.546  45.152  28.128  1.00  59.45      AAAA C
ATOM   2969  CG  ASP   312    37.761  43.671  28.382  1.00  65.64      AAAA C
ATOM   2970  OD1 ASP   312    38.525  43.034  27.636  1.00  72.60      AAAA O
ATOM   2971  OD2 ASP   312    37.154  43.176  29.348  1.00  66.86      AAAA O
ATOM   2972  C   ASP   312    35.589  45.337  29.693  1.00  59.39      AAAA C
ATOM   2973  O   ASP   312    34.729  45.007  28.867  1.00  61.00      AAAA O
ATOM   2974  N   SER   313    35.279  45.290  30.976  1.00  61.17      AAAA N
ATOM   2976  CA  SER   313    34.053  44.683  31.459  1.00  55.73      AAAA C
ATOM   2977  CB  SER   313    34.121  43.201  31.093  1.00  48.22      AAAA C
ATOM   2978  OG  SER   313    34.373  42.514  32.292  1.00  57.89      AAAA O
ATOM   2980  C   SER   313    33.998  44.818  32.971  1.00  57.87      AAAA C
ATOM   2981  O   SER   313    34.802  45.506  33.537  1.00  66.17      AAAA O
ATOM   2982  N   VAL   314    33.001  44.205  33.545  1.00  64.35      AAAA N
ATOM   2984  CA  VAL   314    32.840  44.305  35.013  1.00  64.39      AAAA C
ATOM   2985  CB  VAL   314    31.360  44.340  35.343  1.00  69.57      AAAA C
ATOM   2986  CG1 VAL   314    31.024  43.693  36.691  1.00  65.60      AAAA C
ATOM   2987  CG2 VAL   314    30.927  45.823  35.319  1.00  65.27      AAAA C
ATOM   2988  C   VAL   314    33.492  43.088  35.638  1.00  62.65      AAAA C
ATOM   2989  O   VAL   314    34.029  43.141  36.704  1.00  63.92      AAAA O
ATOM   2990  N   THR   315    33.468  41.878  34.878  1.00  61.82      AAAA N
ATOM   2992  CA  THR   315    34.029  40.752  35.284  1.00  63.44      AAAA C
ATOM   2993  CB  THR   315    33.618  39.628  34.314  1.00  65.54      AAAA C
ATOM   2994  OG1 THR   315    32.403  40.004  33.634  1.00  74.05      AAAA O
ATOM   2996  CG2 THR   315    33.339  38.356  35.104  1.00  64.86      AAAA C
ATOM   2997  C   THR   315    35.541  40.971  35.323  1.00  65.62      AAAA C
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ATOM	2998	O	THR	315	36.217	40.339	36.206	1.00	66.41	AAAA	O
ATOM	2999	N	SER	316	36.071	41.593	34.332	1.00	63.28	AAAA	N
ATOM	3001	CA	SER	316	37.500	41.793	34.215	1.00	58.72	AAAA	C
ATOM	3002	CB	SER	316	37.795	42.557	32.900	1.00	52.20	AAAA	C
ATOM	3003	OG	SER	316	37.298	43.859	32.933	1.00	48.04	AAAA	O
ATOM	3005	C	SER	316	38.077	42.573	35.387	1.00	58.91	AAAA	C
ATOM	3006	O	SER	316	39.293	42.522	35.520	1.00	59.86	AAAA	O
ATOM	3007	N	ALA	317	37.310	43.362	36.111	1.00	55.86	AAAA	N
ATOM	3009	CA	ALA	317	37.750	44.194	37.191	1.00	57.17	AAAA	C
ATOM	3010	CB	ALA	317	36.833	45.409	37.269	1.00	54.23	AAAA	C
ATOM	3011	C	ALA	317	37.689	43.487	38.538	1.00	62.05	AAAA	C
ATOM	3012	O	ALA	317	37.702	44.128	39.599	1.00	60.30	AAAA	O
ATOM	3013	N	GLN	318	37.361	42.205	38.523	1.00	67.91	AAAA	N
ATOM	3015	CA	GLN	318	37.185	41.380	39.713	1.00	70.72	AAAA	C
ATOM	3016	CB	GLN	318	36.857	39.956	39.293	1.00	74.48	AAAA	C
ATOM	3017	CG	GLN	318	36.624	38.947	40.383	1.00	89.82	AAAA	C
ATOM	3018	CD	GLN	318	35.265	39.080	41.048	1.00	92.69	AAAA	C
ATOM	3019	OE1	GLN	318	34.256	38.807	40.391	1.00	98.57	AAAA	O
ATOM	3020	NE2	GLN	318	35.356	39.509	42.308	1.00	92.51	AAAA	N
ATOM	3023	C	GLN	318	38.380	41.413	40.653	1.00	72.63	AAAA	C
ATOM	3024	O	GLN	318	38.294	41.855	41.804	1.00	68.92	AAAA	O
ATOM	3025	N	MET	319	39.562	41.062	40.153	1.00	75.18	AAAA	N
ATOM	3027	CA	MET	319	40.846	41.175	40.826	1.00	71.85	AAAA	C
ATOM	3028	CB	MET	319	41.950	40.960	39.772	1.00	82.00	AAAA	C
ATOM	3029	CG	MET	319	41.740	39.644	39.050	1.00	91.16	AAAA	C
ATOM	3030	SD	MET	319	43.123	38.482	39.185	1.00	106.72	AAAA	S
ATOM	3031	CE	MET	319	42.486	37.105	38.231	1.00	97.56	AAAA	C
ATOM	3032	C	MET	319	41.118	42.509	41.471	1.00	67.68	AAAA	C
ATOM	3033	O	MET	319	41.577	42.541	42.612	1.00	69.73	AAAA	O
ATOM	3034	N	LEU	320	40.740	43.639	40.887	1.00	62.95	AAAA	N
ATOM	3036	CA	LEU	320	40.907	44.938	41.531	1.00	62.31	AAAA	C
ATOM	3037	CB	LEU	320	40.440	46.085	40.623	1.00	54.93	AAAA	C
ATOM	3038	CG	LEU	320	41.091	46.163	39.238	1.00	53.48	AAAA	C
ATOM	3039	CD1	LEU	320	41.005	47.552	38.692	1.00	51.31	AAAA	C
ATOM	3040	CD2	LEU	320	42.557	45.709	39.403	1.00	58.43	AAAA	C
ATOM	3041	C	LEU	320	40.209	45.008	42.881	1.00	60.30	AAAA	C
ATOM	3042	O	LEU	320	40.344	45.969	43.661	1.00	58.72	AAAA	O
ATOM	3043	N	GLN	321	39.267	44.106	43.112	1.00	59.62	AAAA	N
ATOM	3045	CA	GLN	321	38.482	44.128	44.343	1.00	63.50	AAAA	C
ATOM	3046	CB	GLN	321	37.373	43.089	44.250	1.00	62.52	AAAA	C
ATOM	3047	CG	GLN	321	36.611	42.854	45.522	1.00	56.83	AAAA	C
ATOM	3048	CD	GLN	321	35.337	42.064	45.291	1.00	68.77	AAAA	C
ATOM	3049	OE1	GLN	321	35.362	40.969	44.718	1.00	70.37	AAAA	O
ATOM	3050	NE2	GLN	321	34.218	42.632	45.764	1.00	63.77	AAAA	N
ATOM	3053	C	GLN	321	39.367	44.030	45.594	1.00	60.97	AAAA	C
ATOM	3054	O	GLN	321	40.262	43.196	45.782	1.00	57.29	AAAA	O
ATOM	3055	N	GLY	322	39.092	44.928	46.546	1.00	57.62	AAAA	N
ATOM	3057	CA	GLY	322	39.855	44.928	47.790	1.00	60.63	AAAA	C
ATOM	3058	C	GLY	322	41.126	45.773	47.812	1.00	61.78	AAAA	C
ATOM	3059	O	GLY	322	41.584	46.198	48.889	1.00	60.16	AAAA	O
ATOM	3060	N	CYS	323	41.719	46.124	46.528	1.00	60.03	AAAA	N
ATOM	3062	CA	CYS	323	42.938	46.845	46.528	1.00	54.20	AAAA	C
ATOM	3063	C	CYS	323	42.924	48.307	46.910	1.00	53.48	AAAA	C
ATOM	3064	O	CYS	323	42.105	49.148	46.503	1.00	56.43	AAAA	O
ATOM	3065	CB	CYS	323	43.458	46.822	45.096	1.00	53.33	AAAA	C
ATOM	3066	SG	CYS	323	43.325	45.222	44.248	1.00	66.22	AAAA	S
ATOM	3067	N	THR	324	43.994	48.718	47.580	1.00	49.83	AAAA	N
ATOM	3069	CA	THR	324	44.164	50.161	47.811	1.00	52.29	AAAA	C
ATOM	3070	CB	THR	324	44.623	50.324	49.264	1.00	52.84	AAAA	C
ATOM	3071	OG1	THR	324	45.245	49.087	49.634	1.00	59.82	AAAA	O
ATOM	3073	CG2	THR	324	43.130	50.517	50.193	1.00	60.00	AAAA	C
ATOM	3074	C	THR	324	45.154	50.802	46.844	1.00	48.91	AAAA	C
ATOM	3075	O	THR	324	45.277	52.016	46.710	1.00	46.90	AAAA	O
ATOM	3076	N	ILE	325	46.021	49.963	46.254	1.00	46.87	AAAA	N
ATOM	3078	CA	ILE	325	47.114	50.511	45.445	1.00	45.10	AAAA	C
ATOM	3079	CB	ILE	325	48.473	50.577	46.183	1.00	43.60	AAAA	C
ATOM	3080	CG2	ILE	325	49.586	50.905	45.163	1.00	47.47	AAAA	C
ATOM	3081	CG1	ILE	325	48.394	51.623	47.294	1.00	34.03	AAAA	C
ATOM	3082	CD1	ILE	325	49.595	52.010	48.028	1.00	41.94	AAAA	C
ATOM	3083	C	ILE	325	47.265	49.642	44.229	1.00	42.88	AAAA	C
ATOM	3084	O	ILE	325	47.406	48.429	44.469	1.00	42.99	AAAA	O
ATOM	3085	N	PHE	326	47.170	50.239	43.042	1.00	41.19	AAAA	N
ATOM	3087	CA	PHE	326	47.312	49.334	41.880	1.00	42.88	AAAA	C
ATOM	3088	CB	PHE	326	46.166	49.437	40.877	1.00	39.15	AAAA	C
ATOM	3089	CG	PHE	326	46.403	48.474	39.738	1.00	38.03	AAAA	C
ATOM	3090	CD1	PHE	326	46.186	47.125	39.951	1.00	39.68	AAAA	C
ATOM	3091	CD2	PHE	326	46.917	48.892	38.529	1.00	37.31	AAAA	C
ATOM	3092	CE1	PHE	326	46.447	46.139	39.023	1.00	36.52	AAAA	C
ATOM	3093	CE2	PHE	326	47.136	47.919	37.551	1.00	45.74	AAAA	C
ATOM	3094	CZ	PHE	326	46.924	46.570	37.787	1.00	39.92	AAAA	C
ATOM	3095	C	PHE	326	48.682	49.673	41.280	1.00	48.78	AAAA	C
ATOM	3096	O	PHE	326	49.024	50.826	40.966	1.00	51.39	AAAA	O
ATOM	3097	N	LYS	327	49.623	48.751	41.379	1.00	50.22	AAAA	N
ATOM	3099	CA	LYS	327	50.964	49.963	40.831	1.00	51.49	AAAA	C
ATOM	3100	CB	LYS	327	52.050	48.091	41.519	1.00	58.64	AAAA	C

ATOM	3101	CG	LYS	327	53.254	48.997	41.991	1.00 59.15	AAAA C
ATOM	3102	CD	LYS	327	54.528	48.257	41.617	1.00 63.49	AAAA C
ATOM	3103	CE	LYS	327	55.400	48.951	40.592	1.00 68.12	AAAA C
ATOM	3104	NZ	LYS	327	56.260	47.889	39.938	1.00 71.97	AAAA N
ATOM	3108	C	LYS	327	50.895	48.464	39.391	1.00 45.70	AAAA C
ATOM	3109	O	LYS	327	50.901	47.245	39.127	1.00 49.55	AAAA O
ATOM	3110	N	GLY	328	50.760	49.397	38.502	1.00 39.68	AAAA N
ATOM	3112	CA	GLY	328	50.647	49.038	37.080	1.00 39.44	AAAA C
ATOM	3113	C	GLY	328	49.845	50.161	36.427	1.00 39.49	AAAA C
ATOM	3114	O	GLY	328	49.858	51.307	36.881	1.00 31.92	AAAA O
ATOM	3115	N	ASN	329	49.286	49.813	35.289	1.00 41.47	AAAA N
ATOM	3117	CA	ASN	329	48.467	50.750	34.543	1.00 45.72	AAAA C
ATOM	3118	CB	ASN	329	49.185	50.942	33.211	1.00 42.50	AAAA C
ATOM	3119	CG	ASN	329	50.624	51.426	33.357	1.00 42.26	AAAA C
ATOM	3120	OD1	ASN	329	50.954	52.331	34.156	1.00 34.77	AAAA O
ATOM	3121	ND2	ASN	329	51.425	50.769	32.530	1.00 30.62	AAAA N
ATOM	3124	C	ASN	329	47.038	50.207	34.357	1.00 50.37	AAAA C
ATOM	3125	O	ASN	329	46.736	49.015	34.119	1.00 50.17	AAAA O
ATOM	3126	N	LEU	330	46.090	51.143	34.413	1.00 47.13	AAAA N
ATOM	3128	CA	LEU	330	44.691	50.860	34.151	1.00 42.53	AAAA C
ATOM	3129	CB	LEU	330	43.751	51.530	35.153	1.00 42.84	AAAA C
ATOM	3130	CG	LEU	330	43.768	50.995	36.598	1.00 38.65	AAAA C
ATOM	3131	CD1	LEU	330	42.864	51.924	37.417	1.00 38.12	AAAA C
ATOM	3132	CD2	LEU	330	43.283	49.565	36.669	1.00 38.74	AAAA C
ATOM	3133	C	LEU	330	44.352	51.377	32.758	1.00 39.10	AAAA C
ATOM	3134	O	LEU	330	44.509	52.545	32.460	1.00 40.71	AAAA O
ATOM	3135	N	LEU	331	43.933	50.516	31.904	1.00 36.10	AAAA N
ATOM	3137	CA	LEU	331	43.367	50.869	30.625	1.00 43.10	AAAA C
ATOM	3138	CB	LEU	331	43.958	49.894	29.585	1.00 42.29	AAAA C
ATOM	3139	CG	LEU	331	43.301	49.960	28.221	1.00 40.89	AAAA C
ATOM	3140	CD1	LEU	331	43.501	51.319	27.627	1.00 46.64	AAAA C
ATOM	3141	CD2	LEU	331	43.844	48.834	27.367	1.00 48.76	AAAA C
ATOM	3142	C	LEU	331	41.872	50.568	30.705	1.00 41.12	AAAA C
ATOM	3143	O	LEU	331	41.562	49.365	30.779	1.00 40.08	AAAA O
ATOM	3144	N	ILE	332	41.029	51.566	30.862	1.00 41.13	AAAA N
ATOM	3146	CA	ILE	332	39.606	51.241	31.044	1.00 36.90	AAAA C
ATOM	3147	CB	ILE	332	38.885	52.085	32.076	1.00 34.77	AAAA C
ATOM	3148	CG2	ILE	332	37.413	51.612	32.195	1.00 34.66	AAAA C
ATOM	3149	CG1	ILE	332	39.550	51.895	33.452	1.00 33.64	AAAA C
ATOM	3150	CD1	ILE	332	39.479	53.152	34.337	1.00 48.21	AAAA C
ATOM	3151	C	ILE	332	38.959	51.367	29.688	1.00 34.03	AAAA C
ATOM	3152	O	ILE	332	38.867	52.489	29.200	1.00 35.89	AAAA O
ATOM	3153	N	ASN	333	38.569	50.273	29.094	1.00 35.25	AAAA N
ATOM	3155	CA	ASN	333	38.014	50.283	27.737	1.00 40.34	AAAA C
ATOM	3156	CB	ASN	333	38.960	49.499	26.797	1.00 50.50	AAAA C
ATOM	3157	CG	ASN	333	38.668	49.493	25.310	1.00 59.29	AAAA C
ATOM	3158	OD1	ASN	333	37.845	48.711	24.784	1.00 64.54	AAAA O
ATOM	3159	ND2	ASN	333	39.290	50.350	24.467	1.00 45.83	AAAA N
ATOM	3162	C	ASN	333	36.666	49.591	27.755	1.00 47.63	AAAA C
ATOM	3163	O	ASN	333	36.462	48.409	27.398	1.00 44.40	AAAA O
ATOM	3164	N	ILE	334	35.644	50.213	28.315	1.00 54.13	AAAA N
ATOM	3166	CA	ILE	334	34.332	49.537	28.460	1.00 59.07	AAAA C
ATOM	3167	CB	ILE	334	33.788	49.826	29.876	1.00 61.98	AAAA C
ATOM	3168	CG2	ILE	334	32.362	49.355	30.047	1.00 54.04	AAAA C
ATOM	3169	CG1	ILE	334	34.737	49.224	30.915	1.00 60.43	AAAA C
ATOM	3170	CD1	ILE	334	34.346	49.687	32.317	1.00 68.57	AAAA C
ATOM	3171	C	ILE	334	33.271	50.032	27.476	1.00 59.45	AAAA C
ATOM	3172	O	ILE	334	32.726	51.136	27.635	1.00 56.22	AAAA O
ATOM	3173	N	ARG	335	32.919	49.181	26.550	1.00 59.69	AAAA N
ATOM	3175	CA	ARG	335	31.910	49.567	25.573	1.00 73.93	AAAA C
ATOM	3176	CB	ARG	335	32.262	48.903	24.240	1.00 74.44	AAAA C
ATOM	3177	CG	ARG	335	33.729	48.932	23.918	1.00 82.97	AAAA C
ATOM	3178	CD	ARG	335	34.102	49.289	22.500	1.00 86.49	AAAA C
ATOM	3179	NE	ARG	335	34.361	48.040	21.777	1.00 89.83	AAAA N
ATOM	3181	CZ	ARG	335	34.011	47.838	20.496	1.00 93.67	AAAA C
ATOM	3182	NH1	ARG	335	33.409	48.852	19.843	1.00 87.24	AAAA N
ATOM	3185	NH2	ARG	335	34.256	46.674	19.877	1.00 75.31	AAAA N
ATOM	3188	C	ARG	335	30.492	49.233	26.021	1.00 81.52	AAAA C
ATOM	3189	O	ARG	335	29.664	50.115	26.239	1.00 84.11	AAAA O
ATOM	3190	N	ALA	336	30.208	47.953	26.234	1.00 87.51	AAAA N
ATOM	3192	CA	ALA	336	28.878	47.484	26.601	1.00 92.46	AAAA C
ATOM	3193	CB	ALA	336	28.835	45.980	26.633	1.00 94.03	AAAA C
ATOM	3194	C	ALA	336	28.479	48.058	27.953	1.00 96.61	AAAA C
ATOM	3195	O	ALA	336	29.316	48.019	28.855	1.00 96.96	AAAA O
ATOM	3196	N	GLY	337	27.298	48.685	28.039	1.00 99.74	AAAA N
ATOM	3198	CA	GLY	337	26.986	49.385	29.272	1.00103.11	AAAA C
ATOM	3199	C	GLY	337	25.568	49.303	29.763	1.00105.51	AAAA C
ATOM	3200	O	GLY	337	24.801	50.267	29.596	1.00106.64	AAAA O
ATOM	3201	N	ASN	338	25.243	48.146	30.346	1.00105.41	AAAA N
ATOM	3203	CA	ASN	338	23.886	48.017	30.908	1.00106.92	AAAA C
ATOM	3204	CB	ASN	338	23.714	46.689	31.624	1.00109.14	AAAA C
ATOM	3205	CG	ASN	338	24.403	45.544	30.928	1.00112.30	AAAA C
ATOM	3206	OD1	ASN	338	25.598	45.595	30.625	1.00117.94	AAAA O
ATOM	3207	ND2	ASN	338	23.604	44.508	30.683	1.00113.72	AAAA N
ATOM	3210	C	ASN	338	23.790	49.160	31.931	1.00105.84	AAAA C

ATOM	3211	O	ASH	338	23.544	50.345	31.739	1.00	103.97	AAAA	O
ATOM	3212	N	ASH	339	24.290	48.762	33.099	1.00	105.47	AAAA	N
ATOM	3214	CA	ASH	339	24.529	49.740	34.159	1.00	107.19	AAAA	C
ATOM	3215	CB	ASH	339	23.252	49.915	34.945	1.00	109.15	AAAA	C
ATOM	3216	CG	ASH	339	22.777	51.351	35.003	0.01	107.52	AAAA	C
ATOM	3217	OD1	ASH	339	22.715	51.931	36.088	0.01	107.49	AAAA	O
ATOM	3218	HD2	ASH	339	22.441	51.932	33.859	0.01	107.46	AAAA	N
ATOM	3221	C	ASH	339	25.697	49.237	35.007	1.00	106.33	AAAA	C
ATOM	3222	O	ASH	339	25.520	48.390	35.886	1.00	108.82	AAAA	O
ATOM	3223	N	ILE	340	26.897	49.527	34.510	1.00	101.36	AAAA	N
ATOM	3225	CA	ILE	340	28.136	49.101	35.138	1.00	97.43	AAAA	C
ATOM	3226	CB	ILE	340	29.040	48.354	34.151	1.00	93.63	AAAA	C
ATOM	3227	CG2	ILE	340	28.194	47.252	33.489	1.00	99.38	AAAA	C
ATOM	3228	CG1	ILE	340	29.726	49.158	33.070	1.00	85.50	AAAA	C
ATOM	3229	CD1	ILE	340	28.897	49.634	31.915	1.00	92.53	AAAA	C
ATOM	3230	C	ILE	340	28.783	50.357	35.706	1.00	95.32	AAAA	C
ATOM	3231	O	ILE	340	29.472	51.099	34.997	1.00	97.86	AAAA	O
ATOM	3232	N	ALA	341	28.409	50.739	36.915	1.00	89.89	AAAA	N
ATOM	3234	CA	ALA	341	28.892	52.008	37.450	1.00	88.45	AAAA	C
ATOM	3235	CB	ALA	341	28.068	53.201	37.006	1.00	84.56	AAAA	C
ATOM	3236	C	ALA	341	28.786	51.968	38.970	1.00	85.37	AAAA	C
ATOM	3237	O	ALA	341	28.910	52.935	39.690	1.00	86.09	AAAA	O
ATOM	3238	N	SER	342	28.204	50.877	39.386	1.00	84.24	AAAA	N
ATOM	3240	CA	SER	342	27.910	50.601	40.780	1.00	82.05	AAAA	C
ATOM	3241	CB	SER	342	26.426	50.667	41.112	1.00	85.51	AAAA	C
ATOM	3242	OG	SER	342	26.145	51.271	42.361	1.00	86.02	AAAA	O
ATOM	3244	C	SER	342	28.487	49.196	40.965	1.00	76.62	AAAA	C
ATOM	3245	O	SER	342	29.119	48.966	41.964	1.00	71.76	AAAA	O
ATOM	3246	N	GLU	343	28.373	48.409	39.905	1.00	76.23	AAAA	N
ATOM	3248	CA	GLU	343	29.001	47.109	39.820	1.00	74.59	AAAA	C
ATOM	3249	CB	GLU	343	28.595	46.300	38.616	1.00	78.62	AAAA	C
ATOM	3250	CG	GLU	343	27.118	46.105	38.316	1.00	85.33	AAAA	C
ATOM	3251	CD	GLU	343	26.898	45.121	37.169	1.00	92.76	AAAA	C
ATOM	3252	OE1	GLU	343	27.209	43.911	37.310	1.00	96.41	AAAA	O
ATOM	3253	OE2	GLU	343	26.423	45.517	36.082	1.00	98.55	AAAA	O
ATOM	3254	C	GLU	343	30.525	47.319	39.804	1.00	77.75	AAAA	C
ATOM	3255	O	GLU	343	31.273	46.787	40.637	1.00	75.73	AAAA	O
ATOM	3256	N	LEU	344	31.022	48.237	38.966	1.00	75.65	AAAA	N
ATOM	3258	CA	LEU	344	32.415	48.596	38.839	1.00	72.36	AAAA	C
ATOM	3259	CB	LEU	344	32.760	49.697	37.808	1.00	64.33	AAAA	C
ATOM	3260	CG	LEU	344	32.687	49.397	36.311	1.00	50.12	AAAA	C
ATOM	3261	CD1	LEU	344	33.224	50.577	35.519	1.00	57.00	AAAA	C
ATOM	3262	CD2	LEU	344	33.401	48.127	35.905	1.00	51.63	AAAA	C
ATOM	3263	C	LEU	344	32.963	49.130	40.174	1.00	69.74	AAAA	C
ATOM	3264	O	LEU	344	34.079	48.739	40.551	1.00	69.12	AAAA	O
ATOM	3265	N	GLU	345	32.166	49.959	40.822	1.00	63.10	AAAA	N
ATOM	3267	CA	GLU	345	32.555	50.591	42.061	1.00	65.42	AAAA	C
ATOM	3268	CB	GLU	345	31.592	51.714	42.478	1.00	55.59	AAAA	C
ATOM	3269	CG	GLU	345	32.267	52.607	43.486	1.00	68.78	AAAA	C
ATOM	3270	CD	GLU	345	31.324	53.374	44.376	1.00	81.31	AAAA	C
ATOM	3271	OE1	GLU	345	30.614	54.320	43.976	1.00	85.60	AAAA	O
ATOM	3272	OE2	GLU	345	31.237	53.078	45.595	1.00	88.79	AAAA	O
ATOM	3273	C	GLU	345	32.706	49.652	43.255	1.00	63.31	AAAA	C
ATOM	3274	O	GLU	345	33.501	49.913	44.134	1.00	60.06	AAAA	O
ATOM	3275	N	ASH	346	32.151	48.462	43.292	1.00	62.25	AAAA	N
ATOM	3277	CA	ASH	346	32.285	47.403	44.173	1.00	63.82	AAAA	C
ATOM	3278	CB	ASH	346	31.024	46.498	44.095	1.00	61.66	AAAA	C
ATOM	3279	CG	ASH	346	31.110	45.292	45.006	1.00	58.73	AAAA	C
ATOM	3280	OD1	ASH	346	31.188	45.352	46.224	1.00	69.11	AAAA	O
ATOM	3281	HD2	ASH	346	31.155	44.092	44.444	1.00	51.10	AAAA	N
ATOM	3284	C	ASH	346	33.532	46.580	43.870	1.00	63.71	AAAA	C
ATOM	3285	O	ASH	346	33.636	45.336	43.905	1.00	65.65	AAAA	O
ATOM	3286	N	PHE	347	34.419	47.173	43.066	1.00	63.23	AAAA	N
ATOM	3288	CA	PHE	347	35.540	46.411	42.506	1.00	61.39	AAAA	C
ATOM	3289	CB	PHE	347	35.123	45.854	41.170	1.00	61.38	AAAA	C
ATOM	3290	CG	PHE	347	34.457	44.534	41.142	1.00	65.57	AAAA	C
ATOM	3291	CD1	PHE	347	33.090	44.438	40.982	1.00	75.25	AAAA	C
ATOM	3292	CD2	PHE	347	35.148	43.351	41.267	1.00	77.15	AAAA	C
ATOM	3293	CE1	PHE	347	32.425	43.224	40.951	1.00	75.55	AAAA	C
ATOM	3294	CE2	PHE	347	34.512	42.130	41.242	1.00	72.86	AAAA	C
ATOM	3295	CZ	PHE	347	33.152	42.051	41.095	1.00	72.74	AAAA	C
ATOM	3296	C	PHE	347	36.712	47.375	42.440	1.00	57.70	AAAA	C
ATOM	3297	O	PHE	347	37.770	46.820	42.354	1.00	59.92	AAAA	O
ATOM	3298	N	MET	348	36.482	48.676	42.319	1.00	50.56	AAAA	N
ATOM	3300	CA	MET	348	37.500	49.630	41.964	1.00	42.86	AAAA	C
ATOM	3301	CB	MET	348	37.402	50.096	40.493	1.00	31.72	AAAA	C
ATOM	3302	CG	MET	348	37.426	48.933	39.471	1.00	33.42	AAAA	C
ATOM	3303	SD	MET	348	37.566	49.448	37.732	1.00	44.79	AAAA	S
ATOM	3304	CE	MET	348	38.408	50.999	37.791	1.00	59.57	AAAA	C
ATOM	3305	C	MET	348	37.368	50.831	42.867	1.00	45.88	AAAA	C
ATOM	3306	O	MET	348	38.210	51.772	42.901	1.00	43.33	AAAA	O
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ATOM	3309	CA	GLY	349	35.998	51.965	44.504	1.00	49.19	AAAA	C
ATOM	3310	C	GLY	349	36.980	52.189	45.620	1.00	52.77	AAAA	C
ATOM	3311	O	GLY	349	37.033	53.299	46.156	1.00	53.43	AAAA	O

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ATOM   3315  CB  LEU  350   38.873  49.949  47.834  1.00  49.00      AAAA C
ATOM   3316  CG  LEU  350   37.871  50.020  49.031  1.00  50.79      AAAA C
ATOM   3317  CD1 LEU  350   37.705  48.680  49.700  1.00  52.92      AAAA C
ATOM   3318  CD2 LEU  350   38.247  51.106  50.038  1.00  56.11      AAAA C
ATOM   3319  C   LEU  350   40.144  51.727  46.685  1.00  61.34      AAAA C
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ATOM   3325  CG2 ILE  351   43.101  52.416  42.757  1.00  40.01      AAAA C
ATOM   3326  CG1 ILE  351   41.535  50.418  43.058  1.00  36.87      AAAA C
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ATOM   3346  C   VAL  353   46.829  54.233  42.957  1.00  41.41      AAAA C
ATOM   3347  O   VAL  353   46.843  53.003  43.172  1.00  39.19      AAAA O
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ATOM   3352  CG1 VAL  354   47.347  53.896  38.123  1.00  36.72      AAAA C
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ATOM   3354  C   VAL  354   49.043  54.510  40.388  1.00  44.56      AAAA C
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ATOM   3359  CB  THR  355   52.374  52.799  40.653  1.00  42.40      AAAA C
ATOM   3360  OG1 THR  355   52.273  51.744  39.695  1.00  45.30      AAAA O
ATOM   3362  CG2 THR  355   52.210  52.194  42.039  1.00  38.13      AAAA C
ATOM   3363  C   THR  355   51.746  54.339  38.851  1.00  43.84      AAAA C
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ATOM   3374  CG  TYR  357   49.473  55.219  31.812  1.00  33.04      AAAA C
ATOM   3375  CD1 TYR  357   48.333  54.842  31.077  1.00  32.86      AAAA C
ATOM   3376  CE1 TYR  357   48.352  53.779  30.175  1.00  32.83      AAAA C
ATOM   3377  CD2 TYR  357   50.639  54.465  31.606  1.00  34.28      AAAA C
ATOM   3378  CE2 TYR  357   50.706  53.402  30.720  1.00  32.51      AAAA C
ATOM   3379  CZ  TYR  357   49.552  53.068  30.007  1.00  37.26      AAAA C
ATOM   3380  OH  TYR  357   49.726  51.997  29.166  1.00  35.85      AAAA O
ATOM   3382  C   TYR  357   47.582  55.368  34.150  1.00  38.55      AAAA C
ATOM   3383  O   TYR  357   47.458  54.127  34.088  1.00  36.11      AAAA O
ATOM   3384  N   VAL  358   46.593  56.216  33.814  1.00  40.98      AAAA N
ATOM   3386  CA  VAL  358   45.197  55.798  33.639  1.00  38.90      AAAA C
ATOM   3387  CB  VAL  358   44.211  56.502  34.610  1.00  49.15      AAAA C
ATOM   3388  CG1 VAL  358   42.815  55.883  34.484  1.00  33.12      AAAA C
ATOM   3389  CG2 VAL  358   44.748  56.437  36.043  1.00  29.20      AAAA C
ATOM   3390  C   VAL  358   44.760  56.194  32.234  1.00  35.64      AAAA C
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ATOM   3395  CB  LYS  359   44.849  54.707  29.174  1.00  37.40      AAAA C
ATOM   3396  CG  LYS  359   44.340  54.473  27.770  1.00  45.19      AAAA C
ATOM   3397  CD  LYS  359   45.040  55.317  26.750  1.00  43.40      AAAA C
ATOM   3398  CE  LYS  359   45.958  54.402  25.986  1.00  43.56      AAAA C
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ATOM   3407  CA  ILE  360   40.164  55.742  29.333  1.00  40.02      AAAA C
ATOM   3408  CB  ILE  360   39.297  56.804  30.046  1.00  38.10      AAAA C
ATOM   3409  CG2 ILE  360   37.887  56.277  29.932  1.00  39.42      AAAA C
ATOM   3410  CG1 ILE  360   39.769  57.111  31.481  1.00  28.54      AAAA C
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ATOM   3412  C   ILE  360   39.988  55.837  27.833  1.00  39.49      AAAA C
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ATOM   3416  CA   ARG   361    39.472  54.782  25.744  1.00 41.24      AAAA C
ATOM   3417  CB   ARG   361    40.783  54.213  25.148  1.00 47.92      AAAA C
ATOM   3418  CG   ARG   361    40.805  54.203  23.646  1.00 50.39      AAAA C
ATOM   3419  CD   ARG   361    41.943  53.357  23.116  1.00 51.36      AAAA C
ATOM   3420  NE   ARG   361    41.473  51.974  23.263  1.00 50.97      AAAA N
ATOM   3422  CZ   ARG   361    42.297  50.962  23.490  1.00 55.78      AAAA C
ATOM   3423  NH1  ARG   361    43.612  51.074  23.616  1.00 51.63      AAAA N
ATOM   3426  NH2  ARG   361    41.834  49.719  23.631  1.00 54.52      AAAA N
ATOM   3429  C    ARG   361    38.382  53.866  25.246  1.00 42.06      AAAA C
ATOM   3430  O    ARG   361    38.338  52.661  25.499  1.00 39.93      AAAA O
ATOM   3431  N    HIS   362    37.514  54.342  24.373  1.00 46.19      AAAA N
ATOM   3433  CA   HIS   362    36.372  53.555  23.885  1.00 49.34      AAAA C
ATOM   3434  CB   HIS   362    37.000  52.300  23.266  1.00 40.94      AAAA C
ATOM   3435  CG   HIS   362    37.849  52.610  22.084  1.00 42.78      AAAA C
ATOM   3436  CD2  HIS   362    38.049  53.765  21.411  1.00 48.32      AAAA C
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ATOM   3440  NE2  HIS   362    38.923  53.515  20.408  1.00 49.22      AAAA N
ATOM   3442  C    HIS   362    35.295  53.113  24.913  1.00 50.32      AAAA C
ATOM   3443  O    HIS   362    34.686  52.030  24.795  1.00 41.31      AAAA O
ATOM   3444  N    SER   363    35.222  53.875  26.013  1.00 46.96      AAAA N
ATOM   3446  CA   SER   363    34.402  53.456  27.139  1.00 52.19      AAAA C
ATOM   3447  CB   SER   363    35.231  53.837  28.400  1.00 53.73      AAAA C
ATOM   3448  OG   SER   363    35.713  52.558  28.816  1.00 41.72      AAAA O
ATOM   3450  C    SER   363    33.005  54.072  27.046  1.00 49.09      AAAA C
ATOM   3451  O    SER   363    32.653  55.040  27.694  1.00 37.49      AAAA O
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ATOM   3454  CA   HIS   364    30.954  54.173  25.717  1.00 53.66      AAAA C
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ATOM   3460  CE1  HIS   364    32.798  55.533  22.214  1.00 28.57      AAAA C
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ATOM   3468  C    ALA   365    29.318  53.473  29.768  1.00 44.70      AAAA C
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ATOM   3470  N    LEU   366    30.158  54.517  29.762  1.00 40.80      AAAA N
ATOM   3472  CA   LEU   366    30.415  55.243  30.968  1.00 42.21      AAAA C
ATOM   3473  CB   LEU   366    31.885  55.241  31.350  1.00 43.78      AAAA C
ATOM   3474  CG   LEU   366    32.740  54.037  31.667  1.00 51.52      AAAA C
ATOM   3475  CD1  LEU   366    34.192  54.373  32.043  1.00 51.77      AAAA C
ATOM   3476  CD2  LEU   366    32.118  53.305  32.834  1.00 51.17      AAAA C
ATOM   3477  C    LEU   366    29.974  56.687  30.896  1.00 46.36      AAAA C
ATOM   3478  O    LEU   366    30.305  57.248  29.849  1.00 48.40      AAAA O
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ATOM   3490  CB   SER   368    30.658  59.706  36.000  1.00 55.32      AAAA C
ATOM   3491  OG   SER   368    31.300  60.298  37.091  1.00 64.86      AAAA O
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ATOM   3501  CD2  LEU   369    36.207  57.384  33.619  1.00 38.77      AAAA C
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ATOM   3503  O    LEU   369    35.569  57.700  38.595  1.00 59.33      AAAA O
ATOM   3504  N    SER   370    33.437  58.401  38.285  1.00 56.26      AAAA N
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ATOM   3514  CA   PHE   371    33.223  54.643  40.356  1.00 46.29      AAAA C
ATOM   3515  CB   PHE   371    32.952  53.596  39.297  1.00 43.53      AAAA C
ATOM   3516  CG   PHE   371    33.724  53.629  38.012  1.00 56.45      AAAA C
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ATOM   3519  CE1  PHE   371    35.498  52.842  36.570  1.00 59.50      AAAA C
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ATOM	3524	N	LEU	372	35.633	55.305	40.510	1.00	50.17	AAAA N
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ATOM	3527	CB	LEU	372	38.171	55.812	40.276	1.00	44.82	AAAA C
ATOM	3528	CG	LEU	372	38.411	54.800	39.114	1.00	36.78	AAAA C
ATOM	3529	CD1	LEU	372	38.853	55.643	37.934	1.00	45.04	AAAA C
ATOM	3530	CD2	LEU	372	39.260	53.657	39.565	1.00	35.55	AAAA C
ATOM	3531	C	LEU	372	36.715	56.392	42.243	1.00	42.26	AAAA C
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ATOM	3536	CB	LYS	373	34.546	55.521	45.077	1.00	56.74	AAAA C
ATOM	3537	CG	LYS	373	33.645	56.162	46.119	1.00	59.64	AAAA C
ATOM	3538	CD	LYS	373	32.529	56.955	45.441	0.01	60.17	AAAA C
ATOM	3539	CE	LYS	373	31.674	57.687	46.460	0.01	60.45	AAAA C
ATOM	3540	NZ	LYS	373	31.083	58.933	45.899	0.01	60.38	AAAA N
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ATOM	3548	CA	ASN	374	38.765	56.352	46.410	1.00	59.92	AAAA C
ATOM	3549	CB	ASN	374	39.080	55.154	47.314	1.00	63.16	AAAA C
ATOM	3550	CG	ASN	374	38.009	54.978	48.396	1.00	64.53	AAAA C
ATOM	3551	OD1	ASN	374	37.892	53.972	49.096	1.00	66.40	AAAA O
ATOM	3552	ND2	ASN	374	37.160	55.965	48.578	1.00	52.88	AAAA N
ATOM	3555	C	ASN	374	40.043	56.892	45.786	1.00	62.35	AAAA C
ATOM	3556	O	ASN	374	41.031	57.223	46.479	1.00	63.08	AAAA O
ATOM	3557	N	LEU	375	40.091	56.893	44.438	1.00	58.34	AAAA N
ATOM	3559	CA	LEU	375	41.305	57.374	43.795	1.00	54.73	AAAA C
ATOM	3560	CB	LEU	375	41.099	57.359	42.288	1.00	56.41	AAAA C
ATOM	3561	CG	LEU	375	42.396	57.422	41.459	1.00	54.12	AAAA C
ATOM	3562	CD1	LEU	375	43.135	56.112	41.689	1.00	37.88	AAAA C
ATOM	3563	CD2	LEU	375	42.030	57.796	40.041	1.00	40.97	AAAA C
ATOM	3564	C	LEU	375	41.712	58.754	44.245	1.00	52.37	AAAA C
ATOM	3565	O	LEU	375	41.151	59.777	43.877	1.00	52.11	AAAA O
ATOM	3566	N	ARG	376	42.801	58.874	44.982	1.00	55.16	AAAA N
ATOM	3568	CA	ARG	376	43.320	60.155	45.434	1.00	55.45	AAAA C
ATOM	3569	CB	ARG	376	43.706	60.222	46.928	1.00	58.68	AAAA C
ATOM	3570	CG	ARG	376	44.288	58.907	47.415	1.00	69.10	AAAA C
ATOM	3571	CD	ARG	376	44.286	58.817	48.944	1.00	81.17	AAAA C
ATOM	3572	NE	ARG	376	45.377	57.926	49.410	1.00	84.46	AAAA N
ATOM	3574	CZ	ARG	376	46.618	58.380	49.598	1.00	85.64	AAAA C
ATOM	3575	NH1	ARG	376	46.966	59.645	49.383	1.00	81.84	AAAA N
ATOM	3578	NH2	ARG	376	47.571	57.548	50.012	1.00	94.15	AAAA N
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ATOM	3582	O	ARG	376	44.746	61.728	44.465	1.00	44.25	AAAA O
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ATOM	3585	CA	LEU	377	46.526	59.942	43.379	1.00	49.40	AAAA C
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ATOM	3587	CG	LEU	377	48.806	59.577	44.667	1.00	70.76	AAAA C
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ATOM	3589	CD2	LEU	377	49.010	59.696	46.179	1.00	68.60	AAAA C
ATOM	3590	C	LEU	377	47.043	59.022	42.311	1.00	46.33	AAAA C
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ATOM	3594	CA	ILE	378	48.042	58.976	40.042	1.00	49.10	AAAA C
ATOM	3595	CB	ILE	378	47.342	59.303	38.724	1.00	46.36	AAAA C
ATOM	3596	CG2	ILE	378	48.115	58.696	37.574	1.00	34.36	AAAA C
ATOM	3597	CG1	ILE	378	45.871	58.862	38.629	1.00	38.59	AAAA C
ATOM	3598	CD1	ILE	378	44.999	59.515	37.765	1.00	37.18	AAAA C
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ATOM	3604	CB	LEU	379	52.575	57.531	41.054	1.00	48.44	AAAA C
ATOM	3605	CG	LEU	379	52.234	57.363	42.554	1.00	50.28	AAAA C
ATOM	3606	CD1	LEU	379	52.926	56.187	43.217	1.00	39.89	AAAA C
ATOM	3607	CD2	LEU	379	52.616	58.625	43.300	1.00	42.89	AAAA C
ATOM	3608	C	LEU	379	52.609	59.019	39.080	1.00	50.94	AAAA C
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ATOM	3610	N	GLY	380	52.175	58.423	37.972	1.00	48.67	AAAA N
ATOM	3612	CA	GLY	380	52.931	58.715	36.702	1.00	49.94	AAAA C
ATOM	3613	C	GLY	380	54.249	58.155	36.624	1.00	52.70	AAAA C
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ATOM	3618	CB	GLU	381	56.055	55.310	38.323	1.00	45.22	AAAA C
ATOM	3619	CG	GLU	381	55.402	55.779	39.636	1.00	52.91	AAAA C
ATOM	3620	CD	GLU	381	56.050	55.192	40.873	1.00	42.11	AAAA C
ATOM	3621	OE1	GLU	381	56.160	53.966	40.890	1.00	40.26	AAAA O
ATOM	3622	OE2	GLU	381	56.379	56.014	41.754	1.00	51.32	AAAA O
ATOM	3623	C	GLU	381	56.078	55.784	35.859	1.00	55.86	AAAA C
ATOM	3624	O	GLU	381	57.216	55.652	35.346	1.00	54.61	AAAA O

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ATOM   3628  CB  GLU 382    55.051  53.550  33.532  1.00 35.27      AAAA C
ATOM   3629  CG  GLU 382    54.739  53.225  32.051  1.00 49.69      AAAA C
ATOM   3630  CD  GLU 382    54.676  51.719  31.807  1.00 56.45      AAAA C
ATOM   3631  OE1 GLU 382    55.062  50.924  32.705  1.00 61.66      AAAA O
ATOM   3632  OE2 GLU 382    54.264  51.201  30.745  1.00 57.69      AAAA O
ATOM   3633  C   GLU 382    54.006  55.732  32.973  1.00 50.84      AAAA O
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ATOM   3635  N   GLN 383    54.347  56.256  31.780  1.00 52.25      AAAA C
ATOM   3637  CA  GLN 383    53.498  57.153  31.016  1.00 40.15      AAAA C
ATOM   3638  CB  GLN 383    53.914  58.609  31.155  1.00 28.50      AAAA C
ATOM   3639  CG  GLN 383    54.489  58.909  32.542  1.00 31.10      AAAA C
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ATOM   3641  OE1 GLN 383    55.186  60.840  31.683  1.00 40.34      AAAA N
ATOM   3642  NE2 GLN 383    55.043  60.943  33.934  1.00 36.30      AAAA C
ATOM   3645  C   GLN 383    53.426  56.744  29.563  1.00 40.45      AAAA O
ATOM   3646  O   GLN 383    54.131  55.858  29.139  1.00 43.45      AAAA N
ATOM   3647  N   LEU 384    52.375  57.195  28.860  1.00 42.54      AAAA C
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ATOM   3652  CD1 LEU 384    48.611  57.095  28.221  1.00 33.20      AAAA C
ATOM   3653  CD2 LEU 384    49.405  54.968  27.149  1.00 40.51      AAAA O
ATOM   3654  C   LEU 384    53.204  57.809  26.672  1.00 29.66      AAAA N
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ATOM   3662  OE1 GLU 385    53.150  55.213  24.244  1.00 73.13      AAAA O
ATOM   3663  OE2 GLU 385    54.565  53.786  23.301  1.00 47.41      AAAA O
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ATOM   3668  CA  GLY 386    54.181  61.870  24.897  1.00 40.65      AAAA O
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ATOM   3674  CB  ASN 387    55.500  63.084  28.874  1.00 61.51      AAAA O
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ATOM   3677  ND2 ASN 387    58.063  63.251  28.592  1.00 48.46      AAAA O
ATOM   3680  C   ASN 387    53.095  62.100  29.299  1.00 48.99      AAAA N
ATOM   3681  O   ASN 387    52.836  62.891  30.218  1.00 46.29      AAAA C
ATOM   3682  N   TYR 388    52.214  61.116  29.058  1.00 45.09      AAAA C
ATOM   3684  CA  TYR 388    50.846  61.199  29.540  1.00 40.70      AAAA C
ATOM   3685  CB  TYR 388    49.823  60.957  28.399  1.00 42.24      AAAA C
ATOM   3686  CG  TYR 388    49.925  62.056  27.373  1.00 44.38      AAAA C
ATOM   3687  CD1 TYR 388    50.343  61.854  26.064  1.00 35.51      AAAA C
ATOM   3688  CE1 TYR 388    50.401  62.885  25.157  1.00 44.67      AAAA C
ATOM   3689  CD2 TYR 388    49.625  63.356  27.709  1.00 38.14      AAAA C
ATOM   3690  CE2 TYR 388    49.693  64.428  26.830  1.00 41.27      AAAA O
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ATOM   3692  OH  TYR 388    50.151  65.181  24.604  1.00 41.88      AAAA O
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ATOM   3696  N   SER 389    50.020  60.917  31.753  1.00 50.13      AAAA C
ATOM   3698  CA  SER 389    49.591  60.131  32.931  1.00 45.57      AAAA C
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ATOM   3702  C   SER 389    48.097  59.813  32.804  1.00 49.25      AAAA N
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ATOM   3707  CB  PHE 390    45.241  61.581  33.139  1.00 40.53      AAAA C
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ATOM   3709  CD1 PHE 390    43.406  60.273  34.089  1.00 35.59      AAAA C
ATOM   3710  CD2 PHE 390    42.769  62.157  32.748  1.00 47.09      AAAA C
ATOM   3711  CE1 PHE 390    42.050  59.985  34.312  1.00 44.50      AAAA C
ATOM   3712  CE2 PHE 390    41.454  61.824  32.965  1.00 34.54      AAAA C
ATOM   3713  CZ  PHE 390    41.063  60.745  33.739  1.00 38.54      AAAA C
ATOM   3714  C   PHE 390    45.372  60.829  30.720  1.00 40.29      AAAA O
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ATOM   3723  CD2 TYR 391    44.927  58.390  25.584  1.00 47.45      AAAA C
ATOM   3724  CE2 TYR 391    45.157  58.560  24.242  1.00 45.84      AAAA C
ATOM   3725  CZ  TYR 391    46.207  59.350  23.830  1.00 45.84      AAAA C
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ATOM   3730  N    VAL  392    42.417  60.158  27.779  1.00 37.07    AAAA  N
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ATOM   3733  CB   VAL  392    40.075  60.880  28.440  1.00 41.12    AAAA  C
ATOM   3734  CG1  VAL  392    38.612  60.464  28.472  1.00 37.96    AAAA  C
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ATOM   3737  O    VAL  392    40.508  61.277  25.804  1.00 34.71    AAAA  O
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ATOM   3742  CG   LEU  393    41.023  58.649  21.586  1.00 26.48    AAAA  C
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ATOM   3777  C    GLN  396    29.874  59.224  24.458  1.00 48.64    AAAA  C
ATOM   3778  O    GLN  396    29.407  60.287  24.113  1.00 51.63    AAAA  O
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ATOM   3790  N    LEU  398    30.682  59.990  28.001  1.00 55.73    AAAA  N
ATOM   3792  CA   LEU  398    31.312  60.550  29.179  1.00 52.12    AAAA  C
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ATOM   3794  CG   LEU  398    33.606  60.283  30.460  1.00 41.81    AAAA  C
ATOM   3795  CD1  LEU  398    33.417  58.939  31.135  1.00 40.35    AAAA  C
ATOM   3796  CD2  LEU  398    35.070  60.608  30.082  1.00 39.03    AAAA  C
ATOM   3797  C    LEU  398    30.923  61.995  29.353  1.00 52.35    AAAA  C
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ATOM   3814  CB   GLN  400    31.215  64.314  35.049  1.00 54.97    AAAA  C
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ATOM   3816  CD   GLN  400    30.678  63.430  37.389  1.00 65.82    AAAA  C
ATOM   3817  OE1  GLN  400    30.906  64.502  37.962  1.00 68.10    AAAA  O
ATOM   3818  NE2  GLN  400    30.341  62.444  38.222  1.00 55.35    AAAA  N
ATOM   3821  C    GLN  400    33.113  63.008  34.052  1.00 52.08    AAAA  C
ATOM   3822  O    GLN  400    33.107  61.783  33.942  1.00 51.90    AAAA  O
ATOM   3823  N    LEU  401    34.073  63.580  34.751  1.00 49.58    AAAA  N
ATOM   3825  CA   LEU  401    35.175  62.844  35.334  1.00 49.57    AAAA  C
ATOM   3826  CB   LEU  401    36.379  63.903  35.260  1.00 47.94    AAAA  C
ATOM   3827  CG   LEU  401    36.638  64.237  33.772  1.00 46.61    AAAA  C
ATOM   3828  CD1  LEU  401    37.658  65.326  33.677  1.00 39.09    AAAA  C
ATOM   3829  CD2  LEU  401    36.919  63.062  32.869  1.00 40.72    AAAA  C
ATOM   3930  C    LEU  401    34.866  62.357  36.734  1.00 51.23    AAAA  C
ATOM   3931  O    LEU  401    34.258  61.299  36.892  1.00 49.06    AAAA  O
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ATOM	3832	N	TRP	402	35.297	63.140	37.690	1.00 54.58	AAAA N
ATOM	3834	CA	TRP	402	34.975	63.090	39.097	1.00 59.76	AAAA C
ATOM	3835	CB	TRP	402	36.279	62.953	39.933	1.00 59.56	AAAA C
ATOM	3836	CG	TRP	402	36.971	61.624	39.737	1.00 58.17	AAAA C
ATOM	3837	CD2	TRP	402	37.981	61.243	38.784	1.00 53.18	AAAA C
ATOM	3838	CE2	TRP	402	38.286	59.897	39.002	1.00 56.61	AAAA C
ATOM	3839	CE3	TRP	402	38.643	61.917	37.764	1.00 43.25	AAAA C
ATOM	3840	CD1	TRP	402	36.719	60.517	40.459	1.00 53.50	AAAA C
ATOM	3841	NE1	TRP	402	37.488	59.467	40.032	1.00 57.66	AAAA N
ATOM	3843	CZ2	TRP	402	39.212	59.160	38.249	1.00 51.44	AAAA C
ATOM	3844	CZ3	TRP	402	39.546	61.199	37.026	1.00 53.69	AAAA C
ATOM	3845	CH2	TRP	402	39.920	59.857	37.263	1.00 50.79	AAAA C
ATOM	3846	C	TRP	402	34.203	64.389	39.429	1.00 64.09	AAAA C
ATOM	3847	O	TRP	402	34.408	65.449	38.808	1.00 61.98	AAAA O
ATOM	3848	N	ASP	403	33.503	64.418	40.551	1.00 68.85	AAAA N
ATOM	3850	CA	ASP	403	32.947	65.668	41.068	1.00 67.83	AAAA C
ATOM	3851	CB	ASP	403	31.918	65.343	42.151	1.00 72.19	AAAA C
ATOM	3852	CG	ASP	403	30.853	66.417	42.306	1.00 73.08	AAAA C
ATOM	3853	OD1	ASP	403	31.177	67.625	42.297	1.00 71.67	AAAA O
ATOM	3854	OD2	ASP	403	29.693	65.979	42.454	1.00 75.08	AAAA O
ATOM	3855	C	ASP	403	34.005	66.607	41.607	1.00 66.63	AAAA C
ATOM	3856	O	ASP	403	34.245	66.672	42.811	1.00 67.18	AAAA O
ATOM	3857	N	TRP	404	34.449	67.588	40.846	1.00 69.29	AAAA N
ATOM	3859	CA	TRP	404	35.412	68.588	41.291	1.00 77.11	AAAA C
ATOM	3860	CB	TRP	404	35.859	69.409	40.063	1.00 79.10	AAAA C
ATOM	3861	CG	TRP	404	36.504	68.509	39.047	1.00 82.59	AAAA C
ATOM	3862	CD2	TRP	404	37.294	67.346	39.322	1.00 84.82	AAAA C
ATOM	3863	CE2	TRP	404	37.686	66.813	38.081	1.00 84.56	AAAA C
ATOM	3864	CE3	TRP	404	37.793	66.710	40.506	1.00 80.95	AAAA C
ATOM	3865	CD1	TRP	404	36.460	68.622	37.694	1.00 83.37	AAAA C
ATOM	3866	NE1	TRP	404	37.165	67.617	37.111	1.00 80.33	AAAA N
ATOM	3868	CZ2	TRP	404	38.477	65.662	37.982	1.00 85.91	AAAA C
ATOM	3869	CZ3	TRP	404	38.471	65.573	40.392	1.00 86.36	AAAA C
ATOM	3870	CH2	TRP	404	38.860	65.051	39.133	1.00 85.05	AAAA C
ATOM	3871	C	TRP	404	35.034	69.517	42.420	1.00 81.60	AAAA C
ATOM	3872	O	TRP	404	35.387	70.709	42.504	1.00 84.57	AAAA O
ATOM	3873	N	ASP	405	34.281	69.063	43.393	1.00 84.45	AAAA N
ATOM	3875	CA	ASP	405	33.771	69.861	44.496	1.00 87.48	AAAA C
ATOM	3876	CB	ASP	405	32.352	70.365	44.262	1.00 88.04	AAAA C
ATOM	3877	CG	ASP	405	32.274	71.612	43.409	1.00 92.54	AAAA C
ATOM	3878	OD1	ASP	405	33.306	72.285	43.207	1.00 94.82	AAAA O
ATOM	3879	OD2	ASP	405	31.130	71.854	42.955	1.00 95.26	AAAA O
ATOM	3880	C	ASP	405	33.730	68.906	45.693	1.00 87.80	AAAA C
ATOM	3881	O	ASP	405	34.245	69.224	46.743	1.00 92.18	AAAA O
ATOM	3882	N	ALA	406	33.239	67.709	45.460	1.00 84.46	AAAA N
ATOM	3884	CA	ALA	406	33.176	66.671	46.451	1.00 82.87	AAAA C
ATOM	3885	CB	ALA	406	31.943	65.805	46.133	1.00 76.32	AAAA C
ATOM	3886	C	ALA	406	34.445	65.840	46.459	1.00 85.77	AAAA C
ATOM	3887	O	ALA	406	34.470	64.823	47.185	1.00 89.38	AAAA O
ATOM	3888	N	ARG	407	35.433	66.073	45.577	1.00 83.74	AAAA N
ATOM	3890	CA	ARG	407	36.541	65.151	45.400	1.00 79.60	AAAA C
ATOM	3891	CB	ARG	407	36.165	64.140	44.297	1.00 77.84	AAAA C
ATOM	3892	CG	ARG	407	35.457	62.950	44.921	1.00 81.91	AAAA C
ATOM	3893	CD	ARG	407	35.362	61.688	44.113	1.00 86.97	AAAA C
ATOM	3894	NE	ARG	407	36.281	60.660	44.607	1.00 86.94	AAAA N
ATOM	3896	CZ	ARG	407	37.564	60.583	44.279	1.00 92.14	AAAA C
ATOM	3897	NH1	ARG	407	38.169	61.441	43.469	1.00 97.06	AAAA N
ATOM	3900	NH2	ARG	407	38.309	59.616	44.770	1.00 96.33	AAAA N
ATOM	3903	C	ARG	407	37.880	65.749	45.048	1.00 76.72	AAAA C
ATOM	3904	O	ARG	407	37.989	66.774	44.410	1.00 77.47	AAAA O
ATOM	3905	N	ASN	408	38.958	65.081	45.453	1.00 75.75	AAAA N
ATOM	3907	CA	ASN	408	40.311	65.556	45.173	1.00 73.79	AAAA C
ATOM	3908	CB	ASN	408	40.938	66.240	46.388	1.00 74.46	AAAA C
ATOM	3909	CG	ASN	408	41.986	67.242	45.947	1.00 82.51	AAAA C
ATOM	3910	OD1	ASN	408	41.913	68.429	46.240	1.00 90.33	AAAA O
ATOM	3911	ND2	ASN	408	43.028	66.821	45.253	1.00 84.46	AAAA N
ATOM	3914	C	ASN	408	41.257	64.468	44.654	1.00 65.97	AAAA C
ATOM	3915	O	ASN	408	41.251	63.374	45.151	1.00 63.82	AAAA O
ATOM	3916	N	LEU	409	42.041	64.793	43.650	1.00 61.41	AAAA N
ATOM	3918	CA	LEU	409	42.896	63.872	42.947	1.00 60.90	AAAA C
ATOM	3919	CB	LEU	409	42.153	63.250	41.768	1.00 62.98	AAAA C
ATOM	3920	CG	LEU	409	42.902	62.553	40.704	1.00 59.77	AAAA C
ATOM	3921	CD1	LEU	409	43.488	61.205	41.197	1.00 54.06	AAAA C
ATOM	3922	CD2	LEU	409	42.094	62.445	39.486	1.00 55.74	AAAA C
ATOM	3923	C	LEU	409	44.151	64.599	42.485	1.00 61.19	AAAA C
ATOM	3924	O	LEU	409	44.141	65.809	42.370	1.00 60.64	AAAA O
ATOM	3925	N	THR	410	45.281	63.903	42.424	1.00 63.74	AAAA N
ATOM	3927	CA	THR	410	46.589	64.462	42.131	1.00 60.44	AAAA C
ATOM	3928	CB	THR	410	47.454	64.676	43.385	1.00 67.08	AAAA C
ATOM	3929	OG1	THR	410	46.870	65.746	44.157	1.00 74.29	AAAA O
ATOM	3931	CG2	THR	410	48.909	65.103	43.162	1.00 48.56	AAAA C
ATOM	3932	C	THR	410	47.426	63.565	41.218	1.00 56.62	AAAA C
ATOM	3933	O	THR	410	47.382	62.354	41.317	1.00 54.99	AAAA O
ATOM	3934	N	ILE	411	48.077	64.245	40.288	1.00 53.97	AAAA N
ATOM	3936	CA	ILE	411	48.897	63.562	39.291	1.00 53.29	AAAA C

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ATOM	3937	CB	ILE	411	48.409	63.854	37.864	1.00	49.81	AAAA	C
ATOM	3938	CG2	ILE	411	49.216	63.128	36.806	1.00	30.86	AAAA	C
ATOM	3939	CG1	ILE	411	46.911	63.489	37.729	1.00	40.83	AAAA	C
ATOM	3940	CD1	ILE	411	46.322	63.547	36.338	1.00	38.51	AAAA	C
ATOM	3941	C	ILE	411	50.319	64.018	39.569	1.00	55.38	AAAA	C
ATOM	3942	O	ILE	411	50.656	65.179	39.291	1.00	57.59	AAAA	O
ATOM	3943	N	SER	412	51.073	63.182	40.270	1.00	54.26	AAAA	N
ATOM	3945	CA	SER	412	52.434	63.502	40.689	1.00	54.46	AAAA	C
ATOM	3946	CB	SER	412	53.071	62.210	41.248	1.00	55.78	AAAA	C
ATOM	3947	OG	SER	412	53.756	62.536	42.434	1.00	67.12	AAAA	O
ATOM	3949	C	SER	412	53.326	63.910	39.523	1.00	55.52	AAAA	C
ATOM	3950	O	SER	412	54.081	64.876	39.527	1.00	55.04	AAAA	O
ATOM	3951	N	ALA	413	53.254	63.124	38.438	1.00	50.12	AAAA	N
ATOM	3953	CA	ALA	413	54.064	63.402	37.281	1.00	50.01	AAAA	C
ATOM	3954	CB	ALA	413	55.334	62.520	37.365	1.00	34.96	AAAA	C
ATOM	3955	C	ALA	413	53.301	63.078	35.994	1.00	49.71	AAAA	C
ATOM	3956	O	ALA	413	52.495	62.168	35.998	1.00	48.81	AAAA	O
ATOM	3957	N	GLY	414	53.675	63.690	34.895	1.00	47.92	AAAA	N
ATOM	3959	CA	GLY	414	53.057	63.454	33.607	1.00	51.75	AAAA	C
ATOM	3960	C	GLY	414	52.017	64.524	33.294	1.00	52.77	AAAA	C
ATOM	3961	O	GLY	414	51.684	65.370	34.114	1.00	53.23	AAAA	O
ATOM	3962	N	LYS	415	51.385	64.406	32.138	1.00	56.31	AAAA	N
ATOM	3964	CA	LYS	415	50.289	65.317	31.759	1.00	52.49	AAAA	C
ATOM	3965	CB	LYS	415	50.884	66.358	30.833	1.00	50.94	AAAA	C
ATOM	3966	CG	LYS	415	51.198	65.855	29.429	1.00	54.39	AAAA	C
ATOM	3967	CD	LYS	415	52.288	66.691	28.765	1.00	53.96	AAAA	C
ATOM	3968	CE	LYS	415	52.785	66.151	27.441	1.00	56.01	AAAA	C
ATOM	3969	NZ	LYS	415	52.426	67.032	26.284	1.00	66.36	AAAA	N
ATOM	3973	C	LYS	415	49.110	64.576	31.155	1.00	50.04	AAAA	C
ATOM	3974	O	LYS	415	49.077	63.337	31.036	1.00	49.77	AAAA	O
ATOM	3975	N	MET	416	48.091	65.353	30.771	1.00	48.34	AAAA	N
ATOM	3977	CA	MET	416	46.890	64.734	30.186	1.00	46.77	AAAA	C
ATOM	3978	CB	MET	416	45.629	65.186	30.949	1.00	42.79	AAAA	C
ATOM	3979	CG	MET	416	45.836	65.880	32.273	1.00	40.91	AAAA	C
ATOM	3980	SD	MET	416	44.511	65.636	33.517	1.00	56.20	AAAA	S
ATOM	3981	CE	MET	416	44.002	67.366	33.690	1.00	35.94	AAAA	C
ATOM	3982	C	MET	416	46.623	65.064	28.728	1.00	40.40	AAAA	C
ATOM	3983	O	MET	416	46.963	66.137	28.247	1.00	34.84	AAAA	O
ATOM	3984	N	TYR	417	45.893	64.169	28.104	1.00	38.49	AAAA	N
ATOM	3986	CA	TYR	417	45.355	64.387	26.765	1.00	39.50	AAAA	C
ATOM	3987	CB	TYR	417	46.156	63.471	25.831	1.00	32.02	AAAA	C
ATOM	3988	CG	TYR	417	45.583	63.430	24.428	1.00	39.48	AAAA	C
ATOM	3989	CD1	TYR	417	45.730	64.501	23.511	1.00	39.29	AAAA	C
ATOM	3990	CE1	TYR	417	45.196	64.429	22.253	1.00	34.56	AAAA	C
ATOM	3991	CD2	TYR	417	44.884	62.321	24.005	1.00	36.81	AAAA	C
ATOM	3992	CE2	TYR	417	44.379	62.241	22.722	1.00	38.80	AAAA	C
ATOM	3993	CZ	TYR	417	44.535	63.292	21.872	1.00	44.20	AAAA	C
ATOM	3994	OH	TYR	417	44.053	63.361	20.552	1.00	58.10	AAAA	O
ATOM	3996	C	TYR	417	43.853	64.065	26.698	1.00	44.18	AAAA	C
ATOM	3997	O	TYR	417	43.376	62.974	27.135	1.00	42.19	AAAA	O
ATOM	3998	N	PHE	418	43.068	64.971	26.100	1.00	45.84	AAAA	N
ATOM	4000	CA	PHE	418	41.644	64.701	25.910	1.00	45.87	AAAA	C
ATOM	4001	CB	PHE	418	40.772	65.657	26.730	1.00	47.19	AAAA	C
ATOM	4002	CG	PHE	418	40.675	65.264	28.177	1.00	43.44	AAAA	C
ATOM	4003	CD1	PHE	418	41.552	65.685	29.132	1.00	39.43	AAAA	C
ATOM	4004	CD2	PHE	418	39.638	64.417	28.544	1.00	51.21	AAAA	C
ATOM	4005	CE1	PHE	418	41.402	65.291	30.440	1.00	46.44	AAAA	C
ATOM	4006	CE2	PHE	418	39.486	64.023	29.845	1.00	46.63	AAAA	C
ATOM	4007	CZ	PHE	418	40.358	64.454	30.801	1.00	44.68	AAAA	C
ATOM	4008	C	PHE	418	41.251	64.730	24.440	1.00	44.64	AAAA	C
ATOM	4009	O	PHE	418	41.375	65.762	23.812	1.00	47.60	AAAA	O
ATOM	4010	N	ALA	419	40.554	63.713	23.936	1.00	43.06	AAAA	N
ATOM	4012	CA	ALA	419	40.015	63.793	22.607	1.00	39.21	AAAA	C
ATOM	4013	CB	ALA	419	41.090	63.562	21.555	1.00	30.88	AAAA	C
ATOM	4014	C	ALA	419	38.837	62.846	22.366	1.00	41.77	AAAA	C
ATOM	4015	O	ALA	419	38.871	61.628	22.557	1.00	36.08	AAAA	O
ATOM	4016	N	PHE	420	37.829	63.398	21.618	1.00	40.41	AAAA	N
ATOM	4018	CA	PHE	420	36.742	62.621	21.070	1.00	40.03	AAAA	C
ATOM	4019	CB	PHE	420	37.157	61.430	20.180	1.00	45.54	AAAA	C
ATOM	4020	CG	PHE	420	37.832	61.909	18.912	1.00	54.18	AAAA	C
ATOM	4021	CD1	PHE	420	39.221	61.987	18.751	1.00	49.23	AAAA	C
ATOM	4022	CD2	PHE	420	37.006	62.345	17.871	1.00	47.65	AAAA	C
ATOM	4023	CE1	PHE	420	39.783	62.496	17.567	1.00	46.06	AAAA	C
ATOM	4024	CE2	PHE	420	37.572	62.833	16.725	1.00	51.10	AAAA	C
ATOM	4025	CZ	PHE	420	38.964	62.928	16.549	1.00	44.01	AAAA	C
ATOM	4026	C	PHE	420	35.762	62.146	22.126	1.00	41.65	AAAA	C
ATOM	4027	O	PHE	420	35.352	60.991	22.215	1.00	38.35	AAAA	O
ATOM	4028	N	ASN	421	35.459	63.024	23.049	1.00	45.35	AAAA	N
ATOM	4030	CA	ASN	421	34.477	62.960	24.112	1.00	46.86	AAAA	C
ATOM	4031	CB	ASN	421	35.183	63.276	25.449	1.00	43.60	AAAA	C
ATOM	4032	CG	ASN	421	36.407	62.401	25.654	1.00	47.90	AAAA	C
ATOM	4033	OD1	ASN	421	36.426	61.147	25.714	1.00	44.83	AAAA	O
ATOM	4034	ND2	ASN	421	37.541	63.101	25.732	1.00	37.46	AAAA	N
ATOM	4037	C	ASN	421	33.432	64.069	23.835	1.00	47.83	AAAA	C
ATOM	4038	O	ASN	421	33.617	65.233	24.237	1.00	38.95	AAAA	O

ATOM	4039	N	PRO	422	32.453	63.777	22.969	1.00	47.86	AAAA	N
ATOM	4040	CD	PRO	422	32.213	62.423	22.372	1.00	44.11	AAAA	C
ATOM	4041	CA	PRO	422	31.463	64.776	22.605	1.00	47.85	AAAA	C
ATOM	4042	CB	PRO	422	30.731	64.084	21.446	1.00	44.86	AAAA	C
ATOM	4043	CG	PRO	422	30.947	62.623	21.606	1.00	43.01	AAAA	C
ATOM	4044	C	PRO	422	30.577	65.284	23.735	1.00	51.16	AAAA	C
ATOM	4045	O	PRO	422	30.223	66.486	23.744	1.00	48.54	AAAA	O
ATOM	4046	N	LYS	423	30.320	64.487	24.774	1.00	52.90	AAAA	N
ATOM	4048	CA	LYS	423	29.431	64.908	25.865	1.00	58.82	AAAA	C
ATOM	4049	CB	LYS	423	28.556	63.721	26.360	1.00	52.93	AAAA	C
ATOM	4050	CG	LYS	423	28.209	62.810	25.196	1.00	70.55	AAAA	C
ATOM	4051	CD	LYS	423	26.743	62.448	24.996	1.00	73.79	AAAA	C
ATOM	4052	CE	LYS	423	26.030	63.374	24.021	1.00	77.06	AAAA	C
ATOM	4053	NZ	LYS	423	25.949	64.748	24.614	1.00	64.99	AAAA	N
ATOM	4057	C	LYS	423	30.158	65.482	27.071	1.00	57.43	AAAA	C
ATOM	4058	O	LYS	423	29.582	65.478	28.152	1.00	55.22	AAAA	O
ATOM	4059	N	LEU	424	31.425	65.859	26.862	1.00	55.95	AAAA	N
ATOM	4061	CA	LEU	424	32.261	66.162	28.017	1.00	57.07	AAAA	C
ATOM	4062	CB	LEU	424	33.463	65.250	28.237	1.00	49.16	AAAA	C
ATOM	4063	CG	LEU	424	34.390	65.748	29.370	1.00	68.27	AAAA	C
ATOM	4064	CD1	LEU	424	33.821	65.362	30.734	1.00	60.66	AAAA	C
ATOM	4065	CD2	LEU	424	35.825	65.276	29.123	1.00	60.35	AAAA	C
ATOM	4066	C	LEU	424	32.709	67.585	27.878	1.00	56.29	AAAA	C
ATOM	4067	O	LEU	424	33.696	67.861	27.201	1.00	59.98	AAAA	O
ATOM	4068	N	CYS	425	31.995	68.488	28.492	1.00	58.76	AAAA	N
ATOM	4070	CA	CYS	425	32.342	69.916	28.406	1.00	60.39	AAAA	C
ATOM	4071	C	CYS	425	33.771	70.119	28.810	1.00	62.59	AAAA	C
ATOM	4072	O	CYS	425	34.289	69.665	29.831	1.00	64.45	AAAA	O
ATOM	4073	CB	CYS	425	31.249	70.644	29.214	1.00	68.23	AAAA	C
ATOM	4074	SG	CYS	425	29.916	71.303	28.086	1.00	81.03	AAAA	S
ATOM	4075	N	VAL	426	34.529	70.953	28.102	1.00	65.31	AAAA	N
ATOM	4077	CA	VAL	426	35.943	71.149	28.358	1.00	65.49	AAAA	C
ATOM	4078	CB	VAL	426	36.644	72.022	27.310	1.00	66.66	AAAA	C
ATOM	4079	CG1	VAL	426	36.715	71.413	25.925	1.00	62.49	AAAA	C
ATOM	4080	CG2	VAL	426	35.962	73.365	27.239	1.00	60.92	AAAA	C
ATOM	4081	C	VAL	426	36.105	71.711	29.757	1.00	65.99	AAAA	C
ATOM	4082	O	VAL	426	37.180	71.724	30.388	1.00	64.51	AAAA	O
ATOM	4083	N	SER	427	35.090	72.361	30.267	1.00	67.67	AAAA	N
ATOM	4085	CA	SER	427	35.091	72.927	31.599	1.00	66.85	AAAA	C
ATOM	4086	CB	SER	427	33.685	73.499	31.864	1.00	61.16	AAAA	C
ATOM	4087	OG	SER	427	34.088	74.860	32.098	1.00	67.05	AAAA	O
ATOM	4089	C	SER	427	35.515	71.972	32.701	1.00	64.24	AAAA	C
ATOM	4090	O	SER	427	36.332	72.328	33.573	1.00	63.66	AAAA	O
ATOM	4091	N	GLU	428	34.965	70.771	32.618	1.00	58.75	AAAA	N
ATOM	4093	CA	GLU	428	35.384	69.753	33.585	1.00	63.39	AAAA	C
ATOM	4094	CB	GLU	428	34.594	68.485	33.240	1.00	68.67	AAAA	C
ATOM	4095	CG	GLU	428	33.115	68.560	33.537	1.00	66.59	AAAA	C
ATOM	4096	CD	GLU	428	32.785	68.560	35.023	1.00	72.33	AAAA	C
ATOM	4097	OE1	GLU	428	32.729	67.522	35.722	1.00	81.62	AAAA	O
ATOM	4098	OE2	GLU	428	32.581	69.688	35.517	1.00	70.97	AAAA	O
ATOM	4099	C	GLU	428	36.870	69.485	33.429	1.00	61.63	AAAA	C
ATOM	4100	O	GLU	428	37.671	69.696	34.397	1.00	62.03	AAAA	O
ATOM	4101	N	ILE	429	37.265	69.262	32.165	1.00	61.26	AAAA	N
ATOM	4103	CA	ILE	429	38.631	69.038	31.789	1.00	61.09	AAAA	C
ATOM	4104	CB	ILE	429	38.759	68.933	30.263	1.00	59.32	AAAA	C
ATOM	4105	CG2	ILE	429	40.257	68.915	29.895	1.00	45.93	AAAA	C
ATOM	4106	CG1	ILE	429	37.968	67.719	29.794	1.00	57.66	AAAA	C
ATOM	4107	CD1	ILE	429	38.038	67.555	28.285	1.00	53.48	AAAA	C
ATOM	4108	C	ILE	429	39.498	70.166	32.323	1.00	61.90	AAAA	C
ATOM	4109	O	ILE	429	40.592	70.017	32.867	1.00	61.28	AAAA	O
ATOM	4110	N	TYR	430	38.987	71.384	32.200	1.00	65.34	AAAA	N
ATOM	4112	CA	TYR	430	39.729	72.543	32.719	1.00	68.10	AAAA	C
ATOM	4113	CB	TYR	430	39.180	73.822	32.099	1.00	71.02	AAAA	C
ATOM	4114	CG	TYR	430	39.538	74.006	30.639	1.00	75.98	AAAA	C
ATOM	4115	CD1	TYR	430	38.653	73.821	29.599	1.00	77.60	AAAA	C
ATOM	4116	CE1	TYR	430	38.953	73.977	28.270	1.00	75.72	AAAA	C
ATOM	4117	CD2	TYR	430	40.810	74.401	30.260	1.00	75.95	AAAA	C
ATOM	4118	CE2	TYR	430	41.155	74.575	28.937	1.00	74.81	AAAA	C
ATOM	4119	CZ	TYR	430	40.221	74.359	27.952	1.00	78.51	AAAA	C
ATOM	4120	OH	TYR	430	40.564	74.542	26.616	1.00	85.40	AAAA	O
ATOM	4122	C	TYR	430	39.779	72.634	34.241	1.00	63.72	AAAA	C
ATOM	4123	O	TYR	430	40.654	73.321	34.758	1.00	58.26	AAAA	O
ATOM	4124	N	ARG	431	38.819	72.017	34.907	1.00	65.53	AAAA	N
ATOM	4126	CA	ARG	431	38.747	72.043	36.356	1.00	68.15	AAAA	C
ATOM	4127	CB	ARG	431	37.348	71.748	36.898	1.00	73.32	AAAA	C
ATOM	4128	CG	ARG	431	37.345	71.815	38.430	1.00	82.99	AAAA	C
ATOM	4129	CD	ARG	431	37.270	73.279	38.860	1.00	88.39	AAAA	C
ATOM	4130	NE	ARG	431	37.698	73.472	40.258	1.00	92.48	AAAA	N
ATOM	4132	CZ	ARG	431	36.835	73.258	41.259	1.00	94.93	AAAA	C
ATOM	4133	NH1	ARG	431	35.610	72.872	40.872	1.00	87.40	AAAA	N
ATOM	4136	NH2	ARG	431	37.021	73.371	42.567	1.00	95.17	AAAA	N
ATOM	4139	C	ARG	431	39.718	70.986	36.877	1.00	67.75	AAAA	C
ATOM	4140	O	ARG	431	40.637	71.292	37.629	1.00	66.74	AAAA	O
ATOM	4141	N	MET	432	39.501	69.791	36.305	1.00	63.87	AAAA	N
ATOM	4143	CA	MET	432	40.437	68.703	36.652	1.00	64.40	AAAA	C

ATOM	4144	CB	MET	432	40.237	67.522	35.719	1.00	54.25	AAAA C
ATOM	4145	CG	MET	432	41.294	66.426	35.971	1.00	40.18	AAAA C
ATOM	4146	SD	MET	432	40.829	64.925	35.112	1.00	52.21	AAAA S
ATOM	4147	CE	MET	432	41.582	63.681	36.137	1.00	54.99	AAAA C
ATOM	4148	C	MET	432	41.891	69.170	36.626	1.00	64.65	AAAA C
ATOM	4149	O	MET	432	42.530	68.992	37.653	1.00	65.89	AAAA O
ATOM	4150	N	GLU	433	42.331	69.811	35.556	1.00	65.78	AAAA N
ATOM	4152	CA	GLU	433	43.622	70.469	35.510	1.00	69.16	AAAA C
ATOM	4153	CB	GLU	433	43.704	71.506	34.401	1.00	69.58	AAAA C
ATOM	4154	CG	GLU	433	44.121	70.967	33.048	1.00	76.91	AAAA C
ATOM	4155	CD	GLU	433	44.623	72.149	32.242	1.00	82.02	AAAA C
ATOM	4156	OE1	GLU	433	44.718	73.224	32.874	1.00	86.82	AAAA O
ATOM	4157	OE2	GLU	433	44.905	72.050	31.042	1.00	88.26	AAAA O
ATOM	4158	C	GLU	433	44.016	71.219	36.781	1.00	71.29	AAAA C
ATOM	4159	O	GLU	433	45.133	71.083	37.294	1.00	74.29	AAAA O
ATOM	4160	N	GLU	434	43.178	72.120	37.280	1.00	72.93	AAAA N
ATOM	4162	CA	GLU	434	43.505	72.873	38.485	1.00	72.86	AAAA C
ATOM	4163	CB	GLU	434	42.458	73.916	38.840	1.00	81.36	AAAA C
ATOM	4164	CG	GLU	434	41.191	73.956	38.032	1.00	83.34	AAAA C
ATOM	4165	CD	GLU	434	40.191	75.004	38.432	1.00	97.32	AAAA C
ATOM	4166	OE1	GLU	434	39.521	74.929	39.505	1.00	97.34	AAAA O
ATOM	4167	OE2	GLU	434	40.080	75.941	37.583	1.00	99.95	AAAA O
ATOM	4168	C	GLU	434	43.675	71.886	39.632	1.00	71.46	AAAA C
ATOM	4169	O	GLU	434	44.728	71.858	40.251	1.00	78.49	AAAA O
ATOM	4170	N	VAL	435	42.670	71.095	39.926	1.00	66.34	AAAA N
ATOM	4172	CA	VAL	435	42.711	70.129	41.001	1.00	62.49	AAAA C
ATOM	4173	CB	VAL	435	41.451	69.217	40.972	1.00	60.38	AAAA C
ATOM	4174	CG1	VAL	435	41.547	68.214	42.104	1.00	52.32	AAAA C
ATOM	4175	CG2	VAL	435	40.203	70.073	41.029	1.00	50.79	AAAA C
ATOM	4176	C	VAL	435	43.939	69.253	41.018	1.00	60.74	AAAA C
ATOM	4177	O	VAL	435	44.607	69.165	42.034	1.00	62.37	AAAA O
ATOM	4178	N	THR	436	44.282	68.506	39.988	1.00	60.67	AAAA N
ATOM	4180	CA	THR	436	45.335	67.516	39.936	1.00	56.36	AAAA C
ATOM	4181	CB	THR	436	45.199	66.565	38.736	1.00	50.92	AAAA C
ATOM	4182	OG1	THR	436	44.913	67.283	37.503	1.00	47.03	AAAA O
ATOM	4184	CG2	THR	436	44.108	65.526	38.901	1.00	54.38	AAAA C
ATOM	4185	C	THR	436	46.701	68.184	39.930	1.00	60.55	AAAA C
ATOM	4186	O	THR	436	47.714	67.490	40.024	1.00	60.61	AAAA O
ATOM	4187	N	GLY	437	46.836	69.496	39.835	1.00	60.65	AAAA N
ATOM	4189	CA	GLY	437	48.102	70.164	39.749	1.00	59.47	AAAA C
ATOM	4190	C	GLY	437	48.800	69.864	38.424	1.00	64.78	AAAA C
ATOM	4191	O	GLY	437	49.983	70.254	38.245	1.00	62.70	AAAA O
ATOM	4192	N	THR	438	48.112	69.387	37.380	1.00	63.79	AAAA N
ATOM	4194	CA	THR	438	48.731	69.169	36.076	1.00	65.09	AAAA C
ATOM	4195	CB	THR	438	47.967	68.027	35.411	1.00	66.87	AAAA C
ATOM	4196	OG1	THR	438	46.600	68.385	35.731	1.00	62.22	AAAA O
ATOM	4198	CG2	THR	438	48.208	66.659	36.019	1.00	68.74	AAAA C
ATOM	4199	C	THR	438	48.590	70.415	35.220	1.00	66.14	AAAA C
ATOM	4200	O	THR	438	49.003	70.543	34.070	1.00	68.05	AAAA O
ATOM	4201	N	LYS	439	48.089	71.481	35.822	1.00	67.37	AAAA N
ATOM	4203	CA	LYS	439	47.927	72.757	35.154	1.00	71.08	AAAA C
ATOM	4204	CB	LYS	439	47.114	73.708	36.034	1.00	69.23	AAAA C
ATOM	4205	CG	LYS	439	46.677	74.938	35.265	1.00	77.26	AAAA C
ATOM	4206	CD	LYS	439	45.832	75.942	36.014	1.00	81.65	AAAA C
ATOM	4207	CE	LYS	439	44.385	75.475	36.182	1.00	87.39	AAAA C
ATOM	4208	NZ	LYS	439	43.667	76.431	37.100	1.00	93.89	AAAA N
ATOM	4212	C	LYS	439	49.249	73.396	34.752	1.00	73.01	AAAA C
ATOM	4213	O	LYS	439	49.996	73.986	35.541	1.00	74.60	AAAA O
ATOM	4214	N	GLY	440	49.517	73.453	33.441	1.00	73.33	AAAA N
ATOM	4216	CA	GLY	440	50.733	74.167	33.014	1.00	71.39	AAAA C
ATOM	4217	C	GLY	440	51.716	73.204	32.389	1.00	71.20	AAAA C
ATOM	4218	O	GLY	440	52.684	73.659	31.822	1.00	72.70	AAAA O
ATOM	4219	N	ARG	441	51.445	71.908	32.436	1.00	72.99	AAAA N
ATOM	4221	CA	ARG	441	52.343	70.945	31.831	1.00	74.12	AAAA C
ATOM	4222	CB	ARG	441	52.617	69.740	32.716	1.00	69.44	AAAA C
ATOM	4223	CG	ARG	441	51.847	69.695	34.003	1.00	63.34	AAAA C
ATOM	4224	CD	ARG	441	52.060	68.314	34.595	1.00	67.64	AAAA C
ATOM	4225	NE	ARG	441	52.244	68.395	36.030	1.00	61.00	AAAA N
ATOM	4227	CZ	ARG	441	52.326	67.357	36.831	1.00	59.21	AAAA C
ATOM	4228	NH1	ARG	441	52.258	66.117	36.395	1.00	60.57	AAAA N
ATOM	4231	NH2	ARG	441	52.468	67.596	38.128	1.00	72.94	AAAA N
ATOM	4234	C	ARG	441	51.760	70.446	30.511	1.00	73.90	AAAA C
ATOM	4235	O	ARG	441	52.195	70.424	30.012	1.00	74.73	AAAA O
ATOM	4236	N	GLN	442	50.732	71.114	30.043	1.00	74.69	AAAA N
ATOM	4238	CA	GLN	442	49.959	70.646	28.914	1.00	75.13	AAAA C
ATOM	4239	CB	GLN	442	48.457	70.875	29.126	1.00	68.73	AAAA C
ATOM	4240	CG	GLN	442	47.669	69.576	29.195	1.00	71.20	AAAA C
ATOM	4241	CD	GLN	442	47.623	69.028	30.607	1.00	70.98	AAAA C
ATOM	4242	OE1	GLN	442	47.714	67.822	30.868	1.00	78.66	AAAA O
ATOM	4243	NE2	GLN	442	47.477	69.907	31.584	1.00	66.86	AAAA N
ATOM	4246	C	GLN	442	50.326	71.359	27.627	1.00	77.69	AAAA C
ATOM	4247	O	GLN	442	50.227	72.569	27.530	1.00	75.57	AAAA O
ATOM	4248	N	ALA	443	50.474	70.554	26.575	1.00	81.54	AAAA N
ATOM	4250	CA	ALA	443	50.643	71.148	25.236	1.00	82.99	AAAA C
ATOM	4251	CB	ALA	443	51.104	70.118	24.220	1.00	81.69	AAAA C

ATOM	4252	C	ALA	443	49.259	71.706	24.952	1.00 83.73	AAAA C
ATOM	4253	O	ALA	443	48.398	71.744	25.830	1.00 83.87	AAAA C
ATOM	4254	H	LYS	444	48.914	72.052	23.713	1.00 86.20	AAAA H
ATOM	4256	CA	LYS	444	47.559	72.524	23.482	1.00 85.88	AAAA C
ATOM	4257	CB	LYS	444	47.426	73.997	23.128	1.00 83.99	AAAA C
ATOM	4258	CG	LYS	444	46.673	74.734	24.241	1.00 93.60	AAAA C
ATOM	4259	CD	LYS	444	45.883	73.841	25.186	1.00 95.14	AAAA C
ATOM	4260	CE	LYS	444	46.390	73.786	26.614	1.00 97.04	AAAA C
ATOM	4261	HC	LYS	444	45.368	73.090	27.473	1.00 97.22	AAAA H
ATOM	4265	C	LYS	444	46.659	71.779	22.508	1.00 84.20	AAAA C
ATOM	4266	O	LYS	444	45.428	71.901	22.635	1.00 85.63	AAAA O
ATOM	4267	H	GLY	445	47.214	70.734	21.916	1.00 78.85	AAAA H
ATOM	4269	CA	GLY	445	46.368	69.786	21.208	1.00 75.06	AAAA C
ATOM	4270	C	GLY	445	45.803	68.844	22.260	1.00 72.30	AAAA C
ATOM	4271	O	GLY	445	44.963	67.993	21.940	1.00 74.90	AAAA O
ATOM	4272	H	ASP	446	46.300	68.981	23.492	1.00 67.97	AAAA H
ATOM	4274	CA	ASP	446	45.914	68.174	24.642	1.00 62.81	AAAA C
ATOM	4275	CB	ASP	446	46.754	68.552	25.873	1.00 55.24	AAAA C
ATOM	4276	CG	ASP	446	48.213	68.169	25.801	1.00 54.07	AAAA C
ATOM	4277	OD1	ASP	446	48.693	67.385	24.946	1.00 45.08	AAAA O
ATOM	4278	OD2	ASP	446	49.091	68.595	26.593	1.00 50.12	AAAA O
ATOM	4279	C	ASP	446	44.438	68.274	25.016	1.00 58.07	AAAA C
ATOM	4280	O	ASP	446	43.610	67.369	25.127	1.00 55.59	AAAA O
ATOM	4281	H	ILE	447	44.043	69.527	25.226	1.00 54.13	AAAA H
ATOM	4283	CA	ILE	447	42.652	69.822	25.510	1.00 54.09	AAAA C
ATOM	4284	CB	ILE	447	42.505	70.502	26.877	1.00 48.92	AAAA C
ATOM	4285	CG2	ILE	447	41.030	70.663	27.182	1.00 41.02	AAAA C
ATOM	4286	CG1	ILE	447	43.211	69.621	27.932	1.00 52.36	AAAA C
ATOM	4287	CD1	ILE	447	43.468	70.323	29.237	1.00 48.47	AAAA C
ATOM	4288	C	ILE	447	42.027	70.591	24.364	1.00 53.06	AAAA C
ATOM	4289	O	ILE	447	41.718	71.772	24.423	1.00 56.08	AAAA O
ATOM	4290	H	ASN	448	41.625	69.915	23.307	1.00 53.17	AAAA H
ATOM	4292	CA	ASN	448	41.013	70.642	22.202	1.00 54.61	AAAA C
ATOM	4293	CB	ASN	448	41.283	69.982	20.863	1.00 49.17	AAAA C
ATOM	4294	CG	ASN	448	40.415	68.786	20.577	1.00 49.40	AAAA C
ATOM	4295	OD1	ASN	448	39.287	68.977	20.113	1.00 52.34	AAAA O
ATOM	4296	HD2	ASN	448	40.990	67.622	20.871	1.00 52.49	AAAA H
ATOM	4299	C	ASN	448	39.518	70.824	22.402	1.00 56.44	AAAA C
ATOM	4300	O	ASN	448	38.816	69.974	22.939	1.00 55.83	AAAA O
ATOM	4301	H	THR	449	39.071	71.917	21.764	1.00 58.52	AAAA H
ATOM	4303	CA	THR	449	37.682	72.351	21.901	1.00 58.62	AAAA C
ATOM	4304	CB	THR	449	37.497	73.845	22.169	1.00 55.90	AAAA C
ATOM	4305	OG1	THR	449	37.913	74.485	20.943	1.00 68.89	AAAA O
ATOM	4307	CG2	THR	449	38.354	74.352	23.310	1.00 59.06	AAAA C
ATOM	4308	C	THR	449	36.920	72.053	20.628	1.00 56.82	AAAA C
ATOM	4309	O	THR	449	35.750	72.381	20.473	1.00 60.87	AAAA O
ATOM	4310	H	ARG	450	37.539	71.304	19.757	1.00 55.76	AAAA H
ATOM	4312	CA	ARG	450	36.887	70.935	18.507	1.00 54.66	AAAA C
ATOM	4313	CB	ARG	450	37.845	71.179	17.377	1.00 48.33	AAAA C
ATOM	4314	CG	ARG	450	38.385	69.975	16.645	1.00 54.81	AAAA C
ATOM	4315	CD	ARG	450	39.487	70.561	15.696	1.00 44.92	AAAA C
ATOM	4316	HE	ARG	450	40.706	70.719	16.488	1.00 52.49	AAAA H
ATOM	4318	CZ	ARG	450	41.544	69.757	16.882	1.00 39.08	AAAA C
ATOM	4319	HH1	ARG	450	41.176	68.572	16.466	1.00 41.07	AAAA H
ATOM	4322	HH2	ARG	450	42.601	70.001	17.610	1.00 45.18	AAAA H
ATOM	4325	C	ARG	450	36.267	69.553	18.557	1.00 56.82	AAAA C
ATOM	4326	O	ARG	450	35.186	69.303	17.992	1.00 58.15	AAAA O
ATOM	4327	H	ASN	451	36.800	68.583	19.324	1.00 56.66	AAAA H
ATOM	4329	CA	ASN	451	36.107	67.311	19.434	1.00 50.27	AAAA C
ATOM	4330	CB	ASN	451	36.725	66.127	18.760	1.00 48.54	AAAA C
ATOM	4331	CG	ASN	451	38.243	66.143	18.764	1.00 60.51	AAAA C
ATOM	4332	OD1	ASN	451	38.779	66.279	19.855	1.00 53.45	AAAA O
ATOM	4333	HD2	ASN	451	38.707	65.976	17.506	1.00 54.88	AAAA H
ATOM	4336	C	ASN	451	35.849	66.854	20.869	1.00 52.97	AAAA C
ATOM	4337	O	ASN	451	35.330	65.750	21.096	1.00 49.71	AAAA O
ATOM	4338	H	ASN	452	36.126	67.668	21.951	1.00 51.98	AAAA H
ATOM	4340	CA	ASN	452	35.769	67.485	23.229	1.00 55.98	AAAA C
ATOM	4341	CB	ASN	452	36.947	67.873	24.136	1.00 54.62	AAAA C
ATOM	4342	CG	ASN	452	37.936	66.736	24.285	1.00 60.96	AAAA C
ATOM	4343	OD1	ASN	452	37.646	65.633	24.735	1.00 51.30	AAAA O
ATOM	4344	HD2	ASN	452	39.153	67.098	23.855	1.00 56.75	AAAA H
ATOM	4347	C	ASN	452	34.603	68.385	23.688	1.00 58.11	AAAA C
ATOM	4348	O	ASN	452	34.785	69.629	23.657	1.00 55.07	AAAA C
ATOM	4349	H	GLY	453	33.444	67.813	23.985	1.00 55.08	AAAA H
ATOM	4351	CA	GLY	453	32.313	68.658	24.296	1.00 59.47	AAAA C
ATOM	4352	C	GLY	453	31.500	69.269	23.174	1.00 64.95	AAAA C
ATOM	4353	O	GLY	453	30.302	69.603	23.276	1.00 65.71	AAAA O
ATOM	4354	H	GLU	454	31.910	69.109	21.910	1.00 67.44	AAAA H
ATOM	4356	CA	GLU	454	31.266	69.543	20.690	1.00 63.63	AAAA C
ATOM	4357	CB	GLU	454	31.739	68.818	19.401	1.00 53.71	AAAA C
ATOM	4358	CG	GLU	454	32.349	67.430	19.738	1.00 49.50	AAAA C
ATOM	4359	CD	GLU	454	32.368	66.620	18.454	1.00 54.61	AAAA C
ATOM	4360	OE1	GLU	454	31.368	66.637	17.702	0.01 54.10	AAAA O
ATOM	4361	OE2	GLU	454	33.417	66.003	18.160	0.01 54.17	AAAA O
ATOM	4362	C	GLU	454	29.762	69.301	20.767	1.00 65.41	AAAA C

ATOM	4363	O	GLU	454	29.022	70.089	20.169	1.00	67.86	AAAA	O
ATOM	4364	N	ARG	455	29.298	69.187	21.333	1.00	66.45	AAAA	N
ATOM	4366	CA	ARG	455	27.843	67.997	21.371	1.00	69.33	AAAA	C
ATOM	4367	CB	ARG	455	27.449	66.733	20.652	1.00	73.38	AAAA	C
ATOM	4368	CG	ARG	455	28.467	65.913	19.924	1.00	74.27	AAAA	C
ATOM	4369	CD	ARG	455	27.775	64.740	19.240	1.00	79.54	AAAA	C
ATOM	4370	NE	ARG	455	27.301	63.638	20.092	1.00	86.31	AAAA	N
ATOM	4372	CZ	ARG	455	27.802	62.412	20.189	1.00	88.60	AAAA	C
ATOM	4373	NH1	ARG	455	28.990	61.997	19.538	1.00	84.51	AAAA	N
ATOM	4376	NH2	ARG	455	27.025	61.523	21.003	1.00	87.36	AAAA	N
ATOM	4378	C	ARG	455	27.213	67.934	22.756	1.00	67.35	AAAA	C
ATOM	4379	O	ARG	455	26.423	67.025	22.961	1.00	66.26	AAAA	O
ATOM	4380	N	ALA	456	27.499	68.879	23.623	1.00	66.52	AAAA	N
ATOM	4381	CA	ALA	456	26.947	68.906	24.964	1.00	72.01	AAAA	C
ATOM	4383	CB	ALA	456	27.832	68.147	25.939	1.00	61.84	AAAA	C
ATOM	4384	C	ALA	456	26.802	70.379	25.371	1.00	75.25	AAAA	C
ATOM	4385	O	ALA	456	27.706	71.219	25.202	1.00	81.30	AAAA	O
ATOM	4386	N	SER	457	25.653	70.720	25.939	0.50	71.91	AAAA	N
ATOM	4387	CA	SER	457	25.431	72.095	26.358	0.50	69.64	AAAA	C
ATOM	4389	CB	SER	457	23.991	72.247	26.836	0.50	73.30	AAAA	C
ATOM	4390	OG	SER	457	23.422	73.294	26.060	0.50	73.31	AAAA	O
ATOM	4391	C	SER	457	26.418	72.510	27.437	0.50	69.27	AAAA	C
ATOM	4393	O	SER	457	26.458	71.957	28.530	0.50	67.32	AAAA	O
ATOM	4394	N	CYS	458	27.197	73.531	27.117	0.50	70.44	AAAA	N
ATOM	4395	CA	CYS	458	28.287	73.960	27.972	0.50	72.57	AAAA	C
ATOM	4397	C	CYS	458	27.949	75.205	28.757	0.50	72.54	AAAA	C
ATOM	4398	O	CYS	458	27.065	75.128	29.606	0.50	76.63	AAAA	O
ATOM	4399	CB	CYS	458	29.527	74.171	27.089	0.50	75.38	AAAA	C
ATOM	4400	SG	CYS	458	30.844	73.032	27.490	0.50	72.18	AAAA	S
ATOM	4401	N	ALA	459	28.607	76.306	28.441	0.50	70.13	AAAA	N
ATOM	4402	CA	ALA	459	28.445	77.572	29.116	0.50	70.05	AAAA	C
ATOM	4404	CB	ALA	459	27.046	78.149	28.996	0.50	70.57	AAAA	C
ATOM	4405	C	ALA	459	28.826	77.461	30.601	0.50	70.13	AAAA	C
ATOM	4406	O	ALA	459	29.080	78.556	31.154	0.50	69.96	AAAA	O
ATOM	4407	OT	ALA	459	28.855	76.301	31.054	0.50	68.22	AAAA	O
ATOM	4522	C1	NAG	461	59.581	7.102	61.119	1.00	88.13	AAAA	C
ATOM	4524	C2	NAG	461	59.964	7.338	59.697	1.00	91.94	AAAA	C
ATOM	4526	N2	NAG	461	58.738	7.699	58.920	1.00	92.72	AAAA	N
ATOM	4528	C7	NAG	461	58.400	9.020	58.999	1.00	96.97	AAAA	C
ATOM	4529	O7	NAG	461	58.879	9.774	59.726	1.00	98.62	AAAA	O
ATOM	4530	C8	NAG	461	57.323	9.390	58.043	1.00	100.60	AAAA	C
ATOM	4534	C3	NAG	461	60.725	6.225	59.085	1.00	94.77	AAAA	C
ATOM	4536	O3	NAG	461	61.417	6.725	57.930	1.00	98.51	AAAA	O
ATOM	4538	C4	NAG	461	61.873	5.869	60.064	1.00	96.01	AAAA	C
ATOM	4540	O4	NAG	461	62.661	4.821	59.484	1.00	99.20	AAAA	O
ATOM	4542	C5	NAG	461	61.359	5.529	61.474	1.00	95.13	AAAA	C
ATOM	4545	C6	NAG	461	62.465	5.321	62.495	1.00	93.66	AAAA	C
ATOM	4548	O6	NAG	461	62.745	6.364	63.354	1.00	92.13	AAAA	O
ATOM	4544	O5	NAG	461	60.625	6.648	61.949	1.00	91.92	AAAA	O
ATOM	4550	C1	NAG	463	33.054	15.249	72.938	1.00	43.58	AAAA	C
ATOM	4552	C2	NAG	463	31.644	15.282	73.412	1.00	43.62	AAAA	C
ATOM	4554	N2	NAG	463	30.709	14.527	72.541	1.00	42.16	AAAA	N
ATOM	4556	C7	NAG	463	29.912	13.584	73.099	1.00	40.84	AAAA	C
ATOM	4557	O7	NAG	463	29.928	13.406	74.222	1.00	40.10	AAAA	O
ATOM	4558	C8	NAG	463	28.975	12.694	72.394	1.00	35.47	AAAA	C
ATOM	4562	C3	NAG	463	31.150	16.675	73.448	1.00	45.40	AAAA	C
ATOM	4564	O3	NAG	463	29.979	16.555	74.196	1.00	45.99	AAAA	O
ATOM	4566	C4	NAG	463	32.117	17.617	74.171	1.00	50.36	AAAA	C
ATOM	4568	O4	NAG	463	31.596	18.919	73.891	1.00	53.97	AAAA	O
ATOM	4569	C5	NAG	463	33.589	17.477	73.725	1.00	48.50	AAAA	C
ATOM	4572	C6	NAG	463	34.490	17.996	74.742	1.00	48.34	AAAA	C
ATOM	4575	O6	NAG	463	34.906	18.739	75.671	1.00	57.11	AAAA	O
ATOM	4571	O5	NAG	463	33.942	16.120	73.583	1.00	48.58	AAAA	O
ATOM	4576	C1	FUC	464	34.544	19.954	76.083	1.00	81.45	AAAA	C
ATOM	4578	C2	FUC	464	35.179	21.173	75.463	1.00	86.35	AAAA	C
ATOM	4579	O2	FUC	464	35.153	21.169	74.021	1.00	92.94	AAAA	O
ATOM	4582	C3	FUC	464	34.252	22.284	75.945	1.00	86.79	AAAA	C
ATOM	4584	O3	FUC	464	34.691	23.613	75.596	1.00	87.83	AAAA	O
ATOM	4586	C4	FUC	464	33.871	22.274	77.412	1.00	86.67	AAAA	C
ATOM	4588	O4	FUC	464	34.598	23.297	78.115	1.00	87.06	AAAA	O
ATOM	4590	C5	FUC	464	33.921	20.894	78.040	1.00	85.85	AAAA	C
ATOM	4593	C6	FUC	464	34.279	20.768	79.512	1.00	83.37	AAAA	C
ATOM	4592	O5	FUC	464	35.042	20.150	77.425	1.00	82.43	AAAA	O
ATOM	4597	C1	NAG	465	31.575	19.813	74.940	1.00	64.68	AAAA	C
ATOM	4599	C2	NAG	465	31.267	21.207	74.437	1.00	69.57	AAAA	C
ATOM	4601	N2	NAG	465	32.480	21.642	73.690	1.00	71.25	AAAA	N
ATOM	4603	C7	NAG	465	32.401	21.953	72.381	1.00	73.86	AAAA	C
ATOM	4604	O7	NAG	465	31.373	21.835	71.881	1.00	74.80	AAAA	O
ATOM	4605	C8	NAG	465	33.679	22.401	71.787	1.00	76.00	AAAA	C
ATOM	4609	C3	NAG	465	31.050	22.214	75.546	1.00	72.71	AAAA	C
ATOM	4611	O3	NAG	465	30.713	23.517	75.108	1.00	71.03	AAAA	O
ATOM	4613	C4	NAG	465	30.035	21.654	76.560	1.00	75.71	AAAA	C
ATOM	4615	O4	NAG	465	29.993	22.409	77.793	1.00	76.79	AAAA	O
ATOM	4617	C5	NAG	465	30.498	20.238	76.977	1.00	75.45	AAAA	C
ATOM	4620	C6	NAG	465	29.461	19.647	77.930	1.00	75.64	AAAA	C

ATOM	4623	O6	HAG	465	28.385	19.239	77.142	1.00	76.25	AAAA	O
ATOM	4619	O5	HAG	465	30.514	19.425	75.807	1.00	71.44	AAAA	O
ATOM	4625	C1	HAG	467	49.927	11.058	87.926	1.00	96.51	AAAA	C
ATOM	4627	C2	HAG	467	50.538	11.751	89.100	1.00	99.92	AAAA	C
ATOM	4629	H2	HAG	467	49.662	12.898	89.459	1.00101.79		AAAA	H
ATOM	4631	C7	HAG	467	49.299	13.021	90.759	1.00103.63		AAAA	C
ATOM	4632	O7	HAG	467	49.541	12.267	91.586	1.00105.48		AAAA	O
ATOM	4633	C8	HAG	467	48.526	14.239	91.102	1.00105.00		AAAA	C
ATOM	4637	C3	HAG	467	51.967	12.134	88.802	1.00101.03		AAAA	C
ATOM	4639	O3	HAG	467	52.535	12.761	89.949	1.00100.89		AAAA	O
ATOM	4641	C4	HAG	467	52.643	10.771	88.506	1.00101.15		AAAA	O
ATOM	4643	O4	HAG	467	54.067	10.834	88.441	1.00101.35		AAAA	C
ATOM	4645	C5	HAG	467	52.039	10.160	87.219	1.00100.16		AAAA	C
ATOM	4648	C6	HAG	467	52.746	8.852	86.934	1.00	99.75	AAAA	O
ATOM	4651	O6	HAG	467	52.088	7.704	87.302	1.00101.54		AAAA	O
ATOM	4647	O5	HAG	467	50.671	9.918	87.503	1.00	98.59	AAAA	C
ATOM	4653	C1	HAG	469	55.375	46.143	66.863	1.00	48.45	AAAA	C
ATOM	4655	C2	HAG	469	56.601	46.993	66.861	1.00	50.42	AAAA	H
ATOM	4657	H2	HAG	469	57.106	47.015	65.451	1.00	51.50	AAAA	C
ATOM	4659	C7	HAG	469	57.235	48.143	64.746	1.00	48.88	AAAA	O
ATOM	4660	O7	HAG	469	56.849	49.101	65.234	1.00	55.62	AAAA	C
ATOM	4661	C8	HAG	469	57.838	48.134	63.394	1.00	43.70	AAAA	C
ATOM	4665	C3	HAG	469	57.608	46.491	67.844	1.00	49.62	AAAA	O
ATOM	4667	O3	HAG	469	58.640	47.461	68.031	1.00	47.76	AAAA	O
ATOM	4669	C4	HAG	469	56.843	46.263	69.172	1.00	48.47	AAAA	O
ATOM	4671	O4	HAG	469	57.826	45.800	70.134	1.00	50.06	AAAA	C
ATOM	4672	C5	HAG	469	55.847	45.130	68.959	1.00	50.81	AAAA	C
ATOM	4675	C6	HAG	469	55.190	44.720	70.239	1.00	53.92	AAAA	O
ATOM	4678	O6	HAG	469	54.829	45.551	71.193	1.00	56.25	AAAA	O
ATOM	4674	O5	HAG	469	54.914	45.599	68.043	1.00	55.45	AAAA	C
ATOM	4679	C1	FUC	470	53.830	46.395	71.203	1.00	61.17	AAAA	C
ATOM	4681	C2	FUC	470	53.642	47.121	72.534	1.00	59.23	AAAA	O
ATOM	4682	O2	FUC	470	54.861	46.876	73.241	1.00	58.39	AAAA	C
ATOM	4685	C3	FUC	470	53.421	48.429	71.757	1.00	56.30	AAAA	O
ATOM	4687	O3	FUC	470	53.381	49.515	72.637	1.00	61.24	AAAA	C
ATOM	4689	C4	FUC	470	52.245	48.255	70.809	1.00	63.74	AAAA	O
ATOM	4691	O4	FUC	470	51.061	47.904	71.544	1.00	62.20	AAAA	C
ATOM	4693	C5	FUC	470	52.455	47.086	69.828	1.00	59.15	AAAA	C
ATOM	4696	C6	FUC	470	51.462	46.723	68.784	1.00	64.68	AAAA	O
ATOM	4695	O5	FUC	470	52.567	45.889	70.781	1.00	37.00	AAAA	C
ATOM	4700	C1	HAG	471	58.034	46.760	71.149	1.00	40.30	AAAA	C
ATOM	4702	C2	NAG	471	58.977	46.225	72.186	1.00	36.82	AAAA	H
ATOM	4704	H2	HAG	471	58.958	44.787	72.509	1.00	44.21	AAAA	C
ATOM	4706	C7	HAG	471	57.856	44.183	72.903	1.00	51.50	AAAA	O
ATOM	4707	O7	HAG	471	56.892	44.744	72.885	1.00	46.02	AAAA	C
ATOM	4708	C8	HAG	471	58.202	42.814	73.323	1.00	34.50	AAAA	C
ATOM	4712	C3	HAG	471	58.901	47.250	73.291	1.00	35.84	AAAA	O
ATOM	4714	O3	HAG	471	59.698	46.917	74.385	1.00	38.52	AAAA	C
ATOM	4716	C4	HAG	471	59.645	48.488	72.694	1.00	37.44	AAAA	O
ATOM	4718	O4	HAG	471	59.754	49.464	73.694	1.00	36.94	AAAA	C
ATOM	4719	C5	HAG	471	59.056	48.959	71.332	1.00	36.14	AAAA	C
ATOM	4722	C6	HAG	471	60.116	49.692	70.525	1.00	43.49	AAAA	O
ATOM	4725	O6	HAG	471	61.106	50.390	71.080	1.00	34.98	AAAA	O
ATOM	4721	O5	NAG	471	58.853	47.785	70.530	1.00	53.37	AAAA	C
ATOM	4727	C1	HAH	472	61.035	49.984	73.953	1.00	56.72	AAAA	C
ATOM	4729	C2	HAH	472	60.920	51.497	74.260	1.00	62.11	AAAA	O
ATOM	4730	O2	HAH	472	59.924	51.584	75.272	1.00	60.70	AAAA	O
ATOM	4733	C3	HAH	472	62.216	52.031	74.840	1.00	60.70	AAAA	O
ATOM	4735	O3	HAH	472	62.028	53.337	75.383	1.00	55.46	AAAA	C
ATOM	4736	C4	HAH	472	62.787	51.161	75.932	1.00	57.16	AAAA	O
ATOM	4738	O4	HAH	472	64.095	51.595	76.171	1.00	52.10	AAAA	C
ATOM	4740	C5	HAH	472	62.797	49.685	75.511	1.00	50.32	AAAA	C
ATOM	4743	C6	HAH	472	63.458	48.905	76.595	1.00	51.02	AAAA	O
ATOM	4746	O6	HAH	472	62.990	48.969	77.885	1.00	53.33	AAAA	O
ATOM	4742	O5	HAH	472	61.443	49.407	75.200	1.00	72.61	AAAA	C
ATOM	4748	C1	MAN	473	62.594	54.401	74.672	1.00	75.28	AAAA	C
ATOM	4750	C2	HAH	473	62.417	55.679	75.569	1.00	74.98	AAAA	O
ATOM	4751	O2	HAH	473	63.378	56.709	75.348	1.00	78.65	AAAA	C
ATOM	4754	C3	HAH	473	60.977	56.163	75.493	1.00	79.16	AAAA	O
ATOM	4756	O3	HAH	473	60.941	57.447	76.148	1.00	78.70	AAAA	C
ATOM	4758	C4	HAH	473	60.344	56.204	74.114	1.00	78.93	AAAA	O
ATOM	4760	O4	HAH	473	58.983	56.571	74.178	1.00	76.89	AAAA	C
ATOM	4762	C5	HAH	473	60.499	54.802	73.474	1.00	74.73	AAAA	C
ATOM	4765	C6	HAH	473	59.968	54.490	72.091	1.00	71.38	AAAA	O
ATOM	4768	O6	HAH	473	60.239	55.469	71.138	1.00	74.97	AAAA	O
ATOM	4764	O5	HAH	473	61.916	54.562	73.463	1.00	82.09	AAAA	C
ATOM	4408	CB	ALA	479	42.462	74.494	16.374	1.00	91.42	BBBB	C
ATOM	4409	C	ALA	479	40.017	74.702	17.001	1.00	96.11	BBBB	O
ATOM	4410	O	ALA	479	40.393	75.108	18.103	1.00	86.43	BBBB	H
ATOM	4413	H	ALA	479	40.696	74.461	14.624	1.00	89.85	BBBB	C
ATOM	4415	CA	ALA	479	41.033	74.108	16.033	1.00	92.12	BBBB	H
ATOM	4416	H	ALA	480	38.749	74.752	16.610	1.00	91.28	BBBB	C
ATOM	4418	CA	ALA	480	37.684	75.264	17.467	1.00	86.84	BBBB	C
ATOM	4419	CB	ALA	480	37.925	76.731	17.769	1.00	91.39	BBBB	C
ATOM	4420	C	ALA	480	36.306	75.030	16.849	1.00		BBBB	C

ATOM	4421	O	ALA	480	35.413	74.647	17.610	1.00	93.79	BBBB	O
ATOM	4422	N	GLU	481	36.135	75.304	15.564	0.01	89.69	BBBB	N
ATOM	4424	CA	GLU	481	34.832	75.164	14.915	1.00	87.19	BBBB	C
ATOM	4425	CB	GLU	481	34.471	76.492	14.224	0.01	92.74	BBBB	C
ATOM	4426	CG	GLU	481	34.277	77.627	15.220	1.00	99.93	BBBB	C
ATOM	4427	CD	GLU	481	34.067	79.003	14.626	1.00	103.59	BBBB	C
ATOM	4428	OE1	GLU	481	35.011	79.777	14.381	1.00	103.27	BBBB	O
ATOM	4429	OE2	GLU	481	32.792	79.328	14.398	1.00	108.00	BBBB	N
ATOM	4432	C	GLU	481	34.755	73.947	14.005	1.00	85.31	BBBB	C
ATOM	4433	O	GLU	481	33.736	73.508	13.456	1.00	83.41	BBBB	O
ATOM	4434	N	LYS	482	35.849	73.188	13.908	1.00	82.85	BBBB	N
ATOM	4436	CA	LYS	482	35.982	71.990	13.089	1.00	73.49	BBBB	C
ATOM	4437	CB	LYS	482	37.377	71.930	12.480	1.00	73.13	BBBB	C
ATOM	4438	CG	LYS	482	38.287	73.128	12.494	1.00	76.33	BBBB	C
ATOM	4439	CD	LYS	482	39.413	72.968	11.471	1.00	80.62	BBBB	C
ATOM	4440	CE	LYS	482	39.985	74.310	11.027	0.01	76.66	BBBB	C
ATOM	4441	NC	LYS	482	41.252	74.136	10.262	0.01	76.20	BBBB	N
ATOM	4445	C	LYS	482	35.779	70.701	13.872	1.00	67.70	BBBB	C
ATOM	4446	O	LYS	482	35.879	70.744	15.092	1.00	69.99	BBBB	O
ATOM	4447	N	LEU	483	35.530	69.595	13.199	1.00	61.47	BBBB	N
ATOM	4449	CA	LEU	483	35.193	68.356	13.896	1.00	59.03	BBBB	C
ATOM	4450	CB	LEU	483	34.256	67.529	13.039	1.00	55.20	BBBB	C
ATOM	4451	CG	LEU	483	32.779	67.860	12.875	1.00	61.94	BBBB	C
ATOM	4452	CD1	LEU	483	32.405	69.154	13.595	1.00	44.78	BBBB	C
ATOM	4453	CD2	LEU	483	32.433	67.707	11.395	1.00	44.63	BBBB	C
ATOM	4454	C	LEU	483	36.421	67.509	14.229	1.00	59.73	BBBB	C
ATOM	4455	O	LEU	483	36.465	66.709	15.165	1.00	57.22	BBBB	O
ATOM	4456	N	ILE	484	37.345	67.543	13.262	1.00	56.21	BBBB	N
ATOM	4458	CA	ILE	484	38.597	66.800	13.367	1.00	52.58	BBBB	C
ATOM	4459	CB	ILE	484	38.480	65.390	12.870	1.00	50.27	BBBB	C
ATOM	4460	CG2	ILE	484	37.769	65.319	11.524	1.00	44.85	BBBB	C
ATOM	4461	CG1	ILE	484	39.870	64.766	12.756	1.00	39.78	BBBB	C
ATOM	4462	CD1	ILE	484	39.889	63.291	12.404	1.00	30.43	BBBB	C
ATOM	4463	C	ILE	484	39.623	67.645	12.608	1.00	53.49	BBBB	C
ATOM	4464	O	ILE	484	39.158	68.568	11.942	1.00	48.33	BBBB	O
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ATOM	4472	O	SER	485	43.510	66.601	12.740	1.00	46.55	BBBB	O
ATOM	4473	N	GLU	486	44.246	68.389	11.604	1.00	52.16	BBBB	N
ATOM	4475	CA	GLU	486	45.624	67.874	11.509	1.00	59.12	BBBB	C
ATOM	4476	CB	GLU	486	46.547	68.683	10.598	1.00	59.71	BBBB	C
ATOM	4477	CG	GLU	486	46.221	70.162	10.568	1.00	76.75	BBBB	C
ATOM	4478	CD	GLU	486	47.370	71.045	10.983	1.00	80.53	BBBB	C
ATOM	4479	OE1	GLU	486	48.315	70.404	11.472	1.00	91.67	BBBB	O
ATOM	4480	OE2	GLU	486	47.480	72.289	10.897	1.00	86.00	BBBB	O
ATOM	4481	C	GLU	486	46.272	67.773	12.896	1.00	56.50	BBBB	C
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ATOM	4497	CG	ASP	488	42.047	66.008	16.267	1.00	45.27	BBBB	C
ATOM	4498	OD1	ASP	488	42.114	66.563	17.387	1.00	56.45	BBBB	O
ATOM	4499	OD2	ASP	488	41.153	66.399	15.492	1.00	55.11	BBBB	O
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ATOM	4501	O	ASP	488	44.967	63.042	15.634	1.00	57.00	BBBB	O
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ATOM	4772	O2	SUL	493	37.611	-7.873	64.920	1.00	110.21	DDDD	O
ATOM	4773	O3	SUL	493	36.533	-8.555	65.856	1.00	109.93	DDDD	O
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ATOM	4781	O1	SUL	495	35.274	12.213	76.595	1.00	111.38	DDDD	O
ATOM	4782	O2	SUL	495	35.476	10.329	74.974	1.00	113.60	DDDD	O
ATOM	4783	O3	SUL	495	33.552	11.860	74.748	1.00	112.77	DDDD	O
ATOM	4784	O4	SUL	495	33.773	10.278	76.604	1.00	113.18	DDDD	O
ATOM	4785	S	SUL	496	35.466	24.844	59.093	1.00	50.73	DDDD	S
ATOM	4786	O1	SUL	496	35.613	24.843	60.607	1.00	62.59	DDDD	O
ATOM	4787	O2	SUL	496	36.002	23.581	58.571	1.00	48.59	DDDD	O
ATOM	4788	O3	SUL	496	35.880	26.084	58.455	1.00	56.74	DDDD	O
ATOM	4789	O4	SUL	496	33.958	24.953	59.034	1.00	59.34	DDDD	O
ATOM	4790	S	SUL	497	47.653	-2.303	70.199	1.00	68.98	DDDD	S
ATOM	4791	O1	SUL	497	47.849	-1.058	70.996	1.00	68.52	DDDD	O
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ATOM	4802	O2	SUL	499	42.089	27.608	69.835	1.00	75.15	DDDD	O
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ATOM	4813	OW	WAT	502	42.522	18.998	78.232	1.00	55.27	DDDD	O
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ATOM	4864	OW	WAT	519	30.644	68.108	30.765	1.00	82.28	DDDD	O
ATOM	4867	OW	WAT	520	38.739	54.257	43.611	1.00	43.41	DDDD	O
ATOM	4870	OW	WAT	521	22.896	4.470	64.871	1.00	48.71	DDDD	O
ATOM	4873	OW	WAT	522	30.939	50.249	19.364	1.00	54.00	DDDD	O
ATOM	4876	OW	WAT	523	32.413	9.061	42.441	1.00	44.45	DDDD	O
ATOM	4879	OW	WAT	524	41.019	42.560	55.653	1.00	43.40	DDDD	O
ATOM	4882	OW	WAT	525	54.268	51.393	37.513	1.00	55.10	DDDD	O
ATOM	4885	OW	WAT	526	37.130	13.599	81.397	1.00	46.49	DDDD	O
ATOM	4888	OW	WAT	527	42.585	10.244	84.472	1.00	35.95	DDDD	O
ATOM	4891	OW	WAT	528	43.661	61.633	18.450	1.00	41.05	DDDD	O
ATOM	4894	OW	WAT	529	27.980	19.862	53.348	1.00	54.59	DDDD	O
ATOM	4897	OW	WAT	530	59.527	38.520	64.116	1.00	37.96	DDDD	O
ATOM	4900	OW	WAT	531	22.451	1.046	57.437	1.00	59.31	DDDD	O
ATOM	4903	OW	WAT	532	30.360	16.123	70.205	1.00	40.39	DDDD	O
ATOM	4906	OW	WAT	533	46.835	27.888	65.854	1.00	52.34	DDDD	O
ATOM	4909	OW	WAT	534	39.446	49.001	45.379	1.00	46.05	DDDD	O
ATOM	4912	OW	WAT	535	46.992	51.272	50.722	1.00	52.62	DDDD	O
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ATOM	4936	OW	WAT	543	41.726	-5.156	65.290	1.00	60.67	DDDD	O
ATOM	4939	OW	WAT	544	48.564	37.335	72.612	1.00	71.69	DDDD	O
ATOM	4942	OW	WAT	545	49.501	40.030	67.582	1.00	44.88	DDDD	O
ATOM	4945	OW	WAT	546	54.851	7.987	60.018	1.00	49.91	DDDD	O

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PCT/AU98/00998

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ATOM   1948  ON   WAT   547    30.459 -14.059  70.554  1.00 84.42    DDDD O
ATOM   1951  ON   WAT   548    57.310  32.779  60.848  1.00 50.77    DDDD O
END
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Face 1 | Cleft 1 | Face 2 | Cleft 2 | Face 3

(12D)
(35S) 11N 10R 8D (6G) 5P
(61A) 33L 32L 30H 28Y (27G) 26E 255I 259E 261S 262D 305E 310T
59R 58F 56L 54Y 53E 242E 241F 256L 263S 264E 309K 312D 335R
91E 90F 82F (274M) 266F 275Q 276E (283R) (302C) 319M (316S) 313S
115K 114E (88V) 83Y 80K 79W 272E 279S 282I 300K 318Q 315T 336R
(140V) 112R 85Y 84N 108R 240R 280G) 298C (322G) 321Q 347F 314V (344V)
138Y 270D 346Q 343E 338N

Figure 2

(a)

(b)

Figure 3

Figure 4

Figure 5

a

IGF1R L1 1
IR   L1 1
EGFR L1 1
EGFR L2 311
IR   L2 310
IGF1R L2 300

K (2) P M

W   S K
W   D

b

IGF1R   150
IR   157
EGFR D2 165
EGFR D4 480

Module 1

Module 2   Module 3   Module 4

Module 5   Module 6

Module 7   Module 8
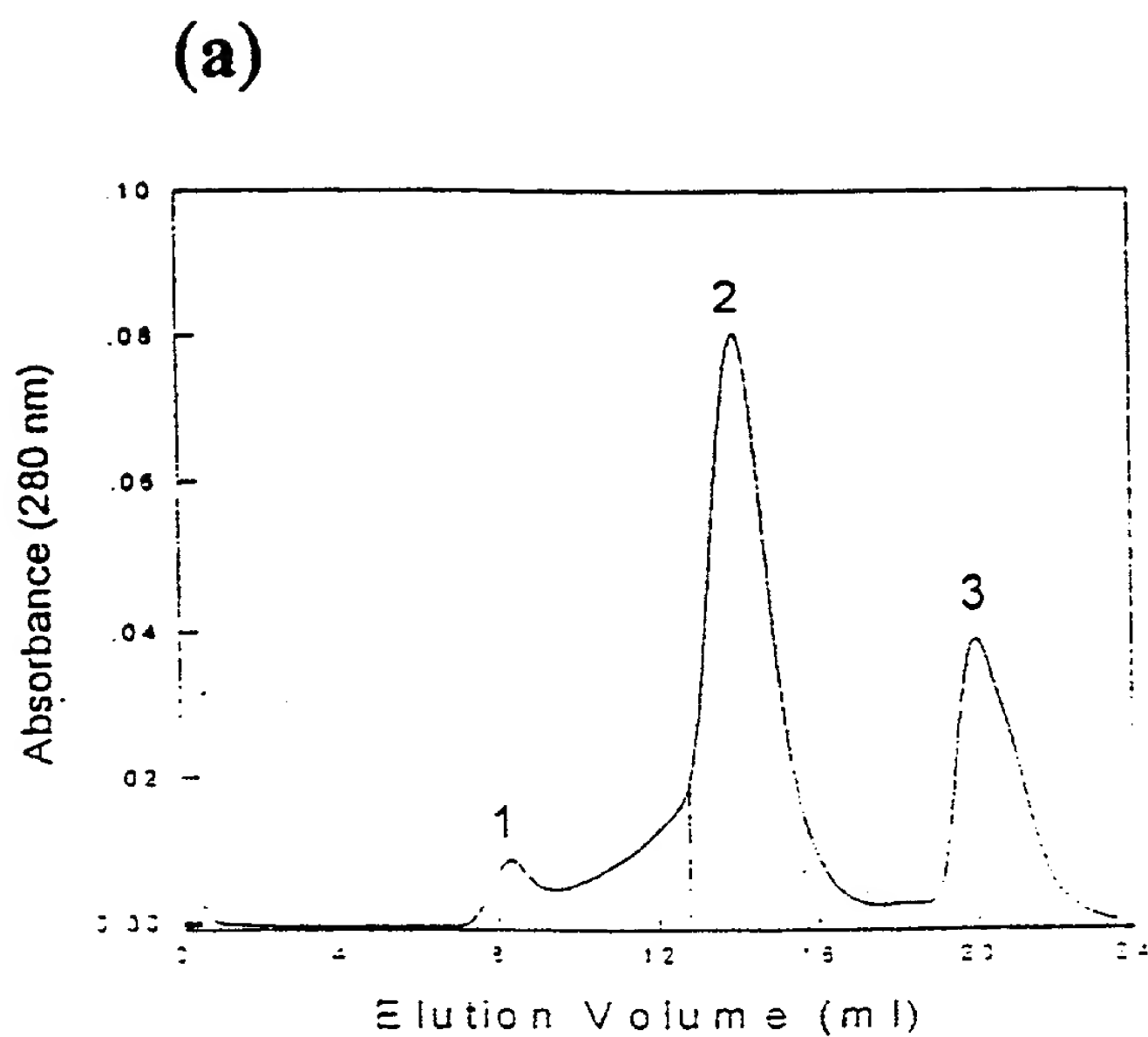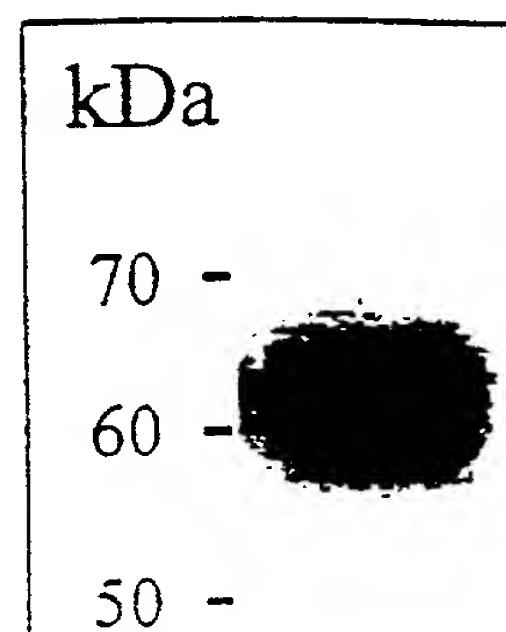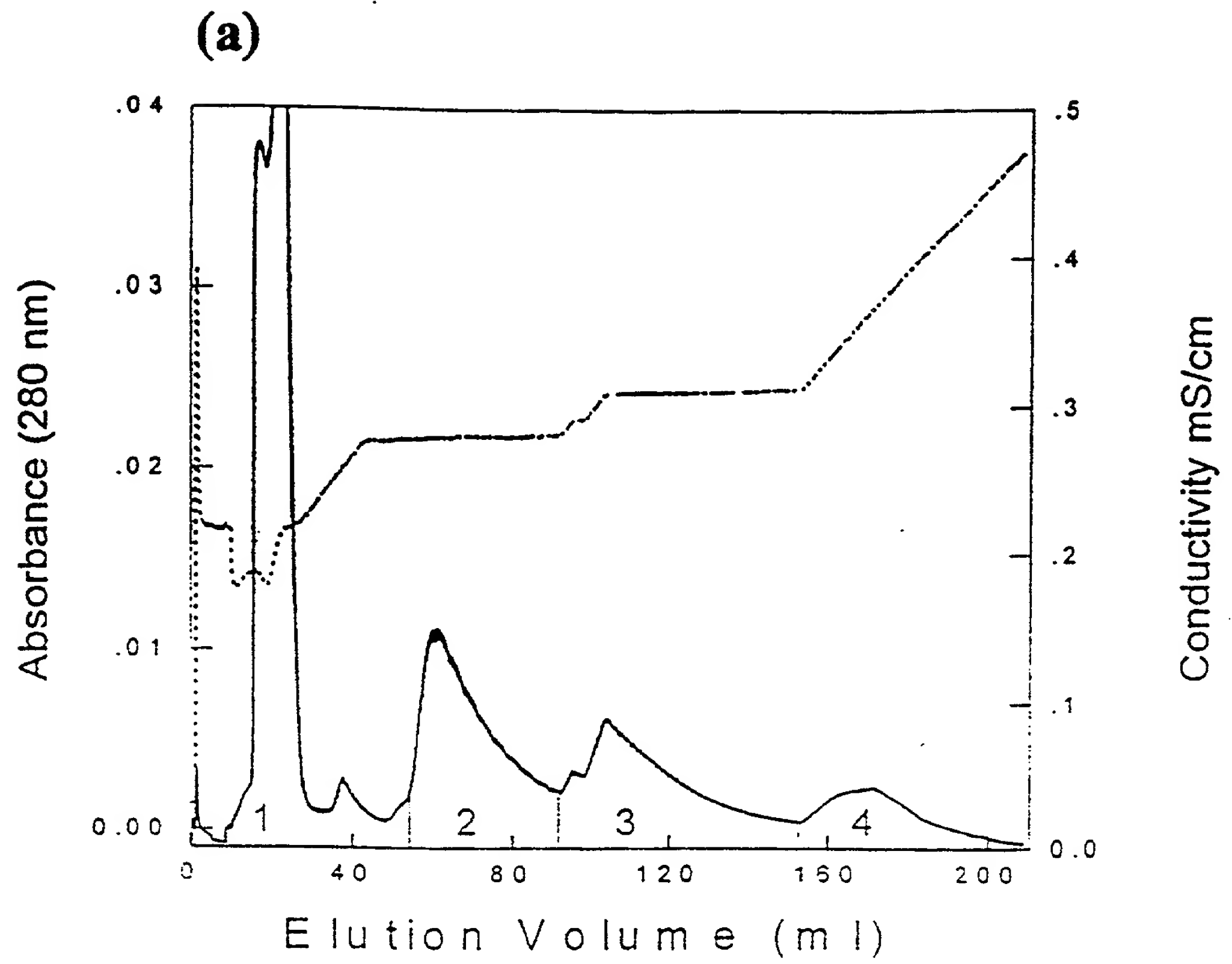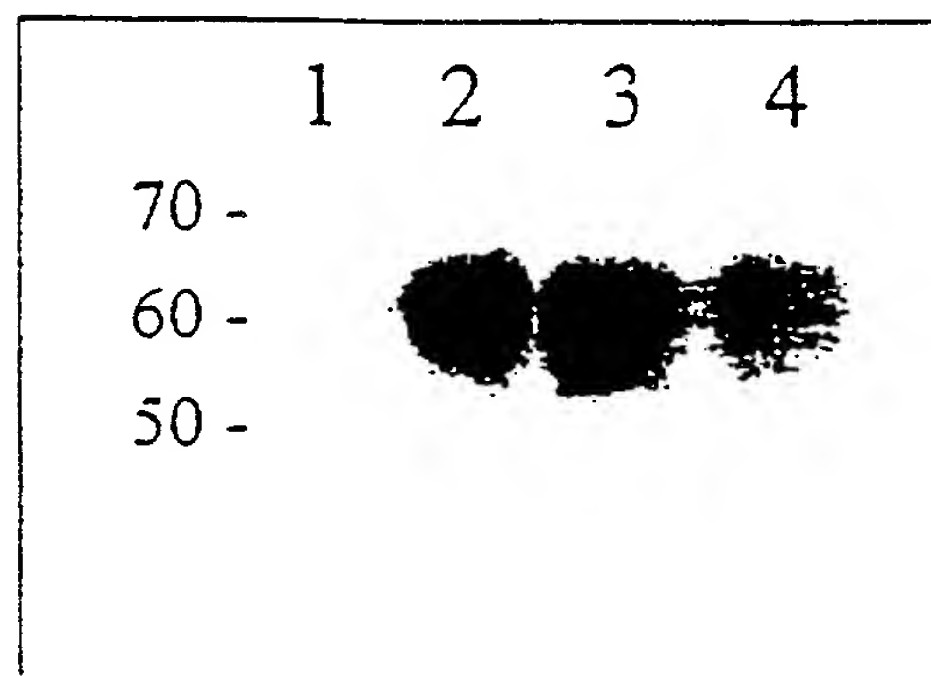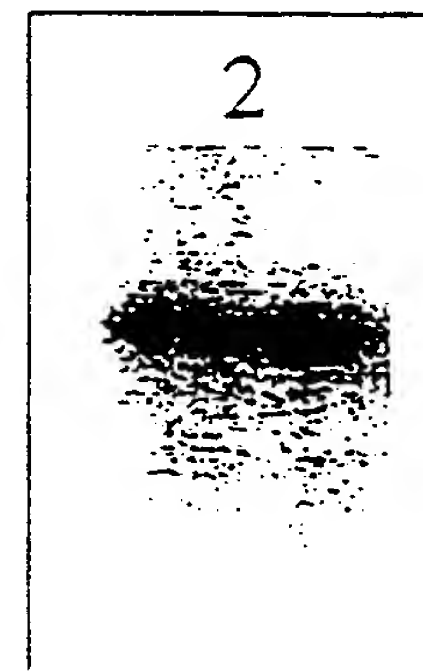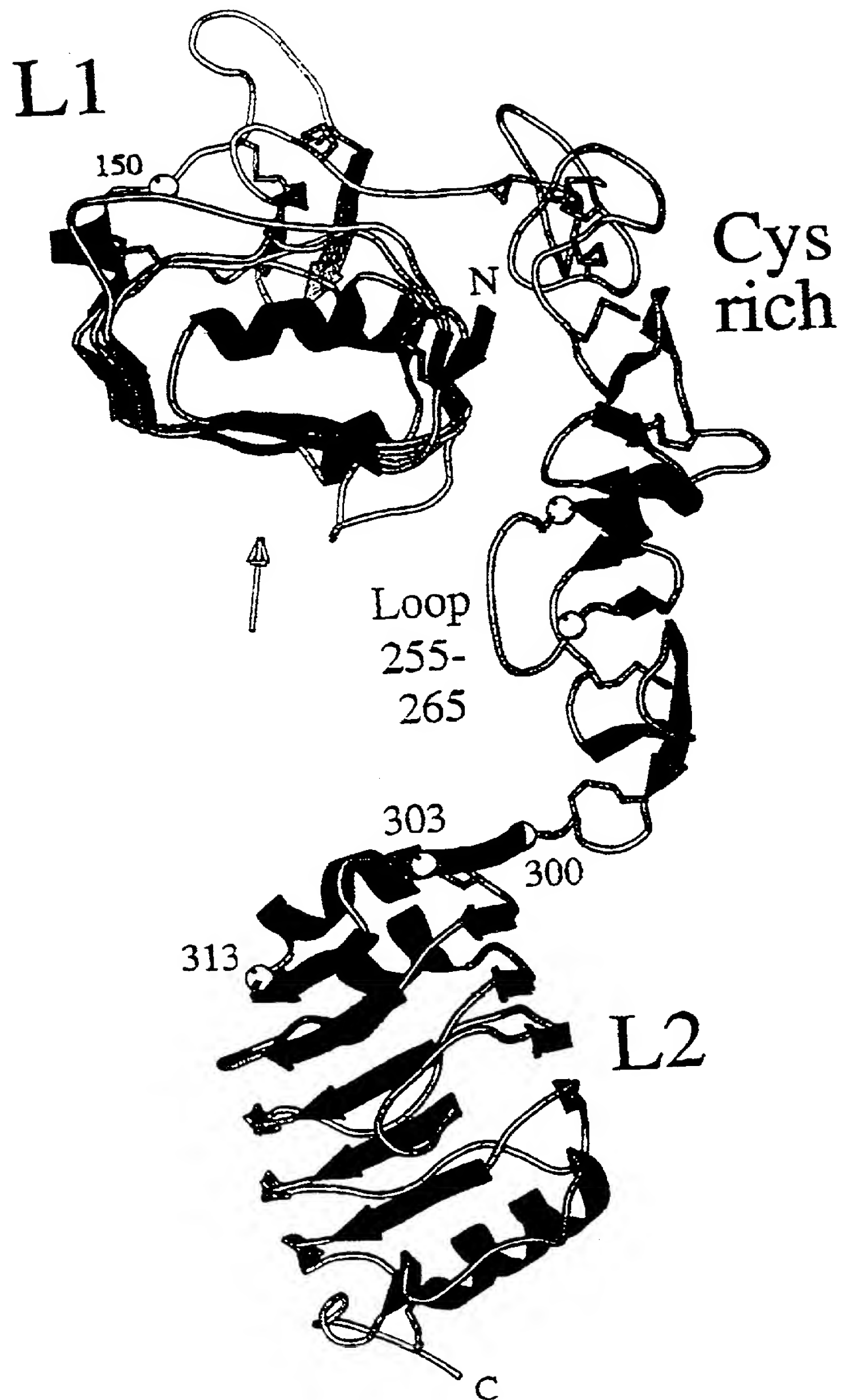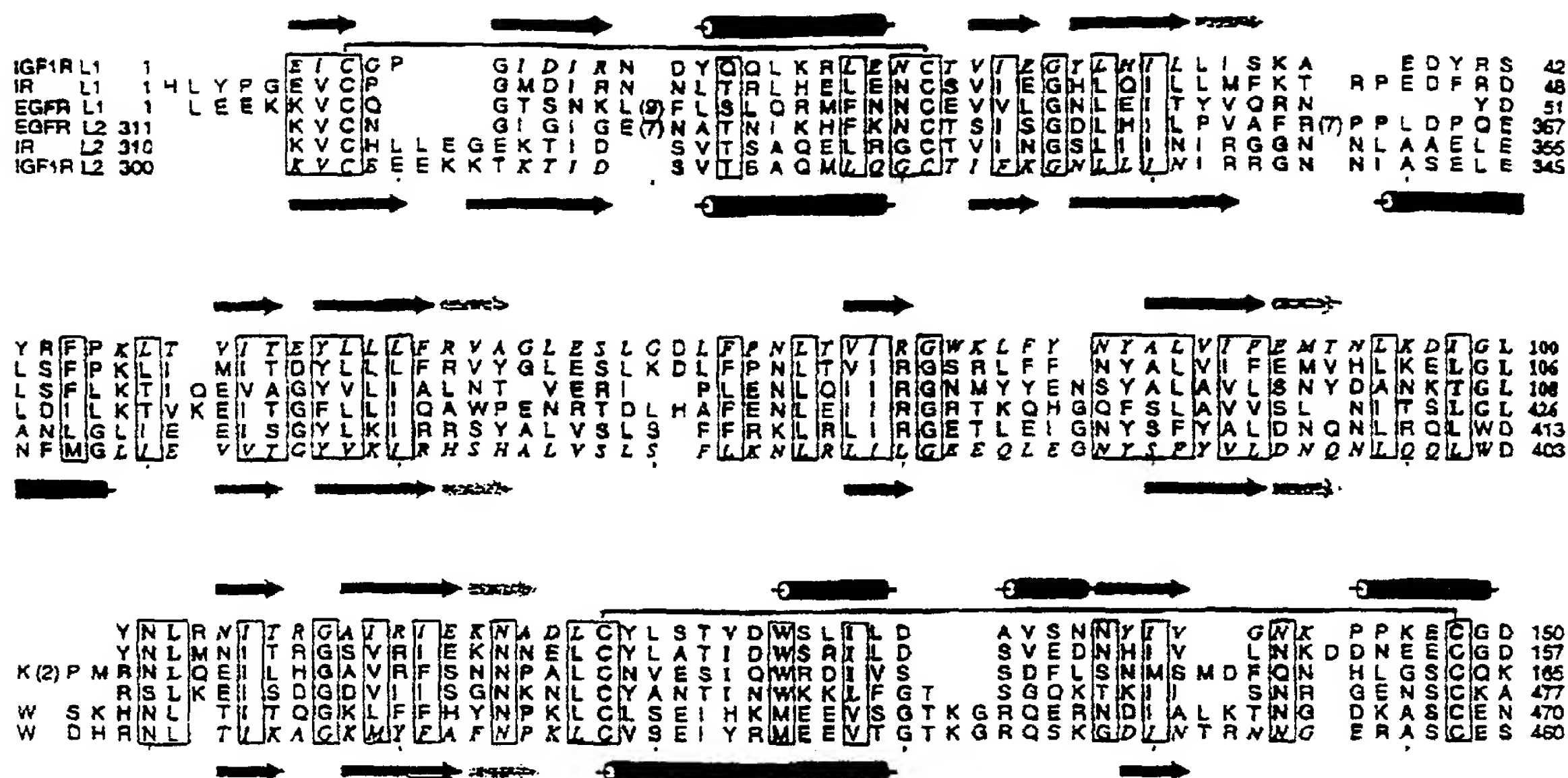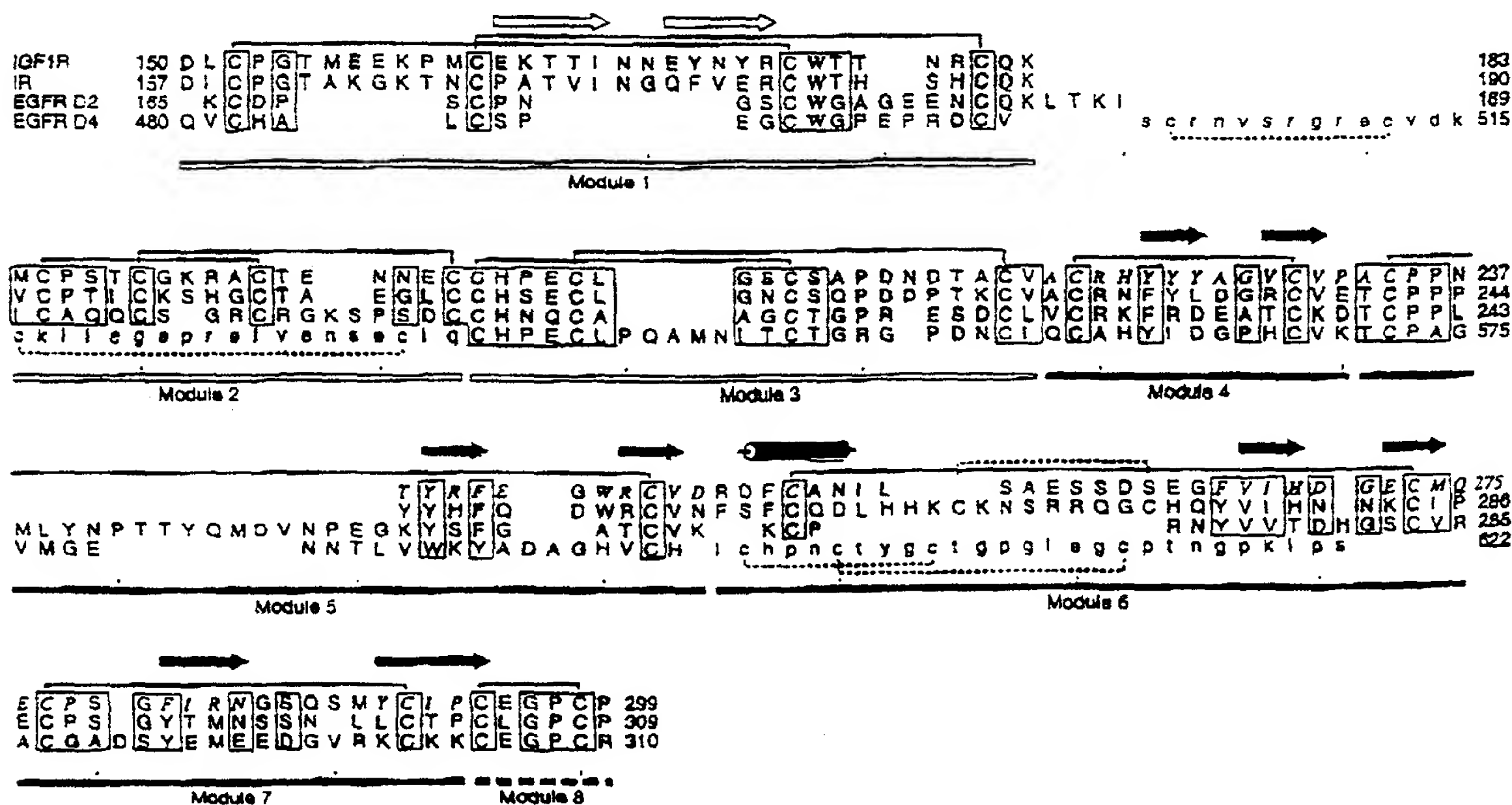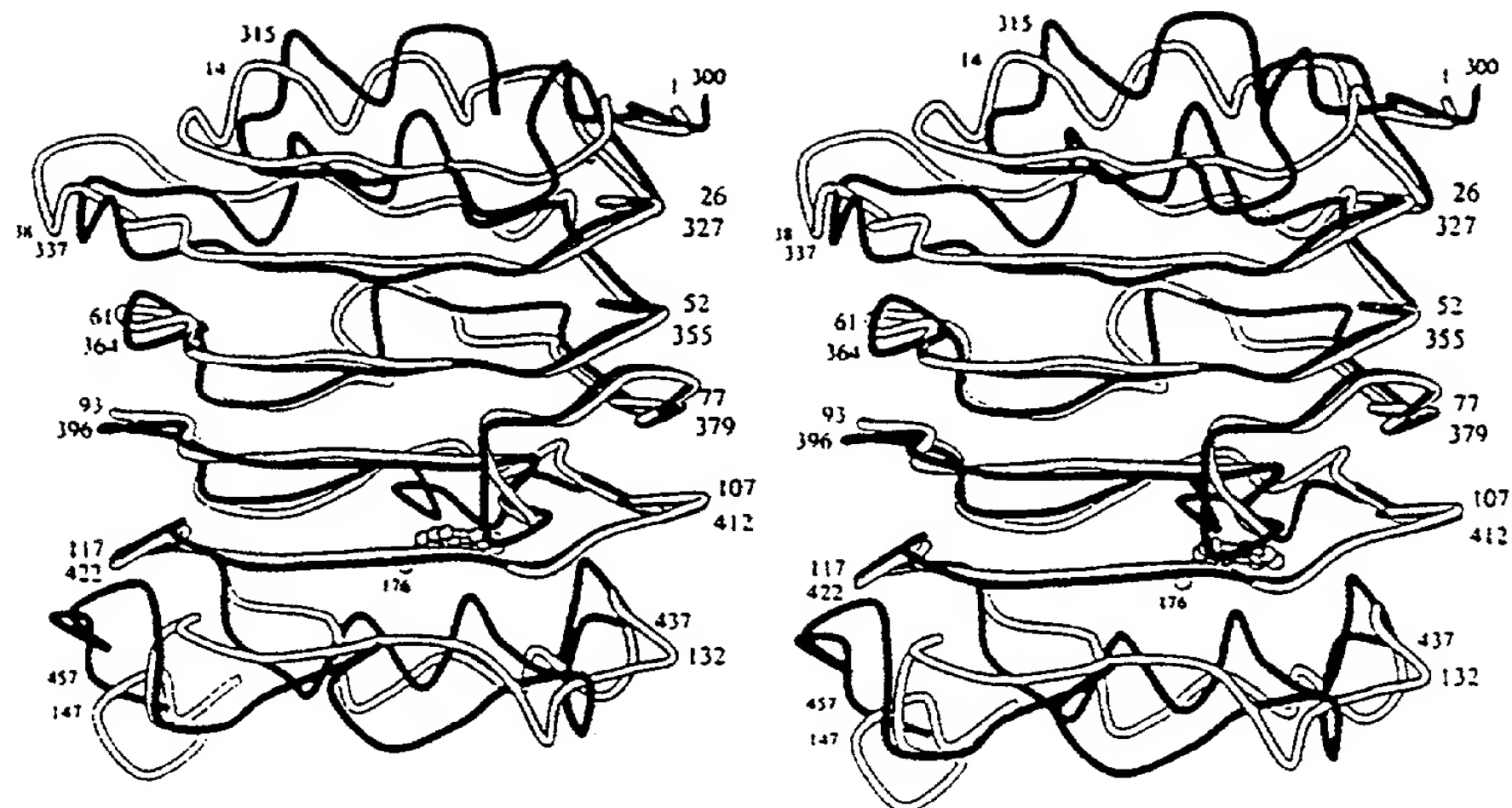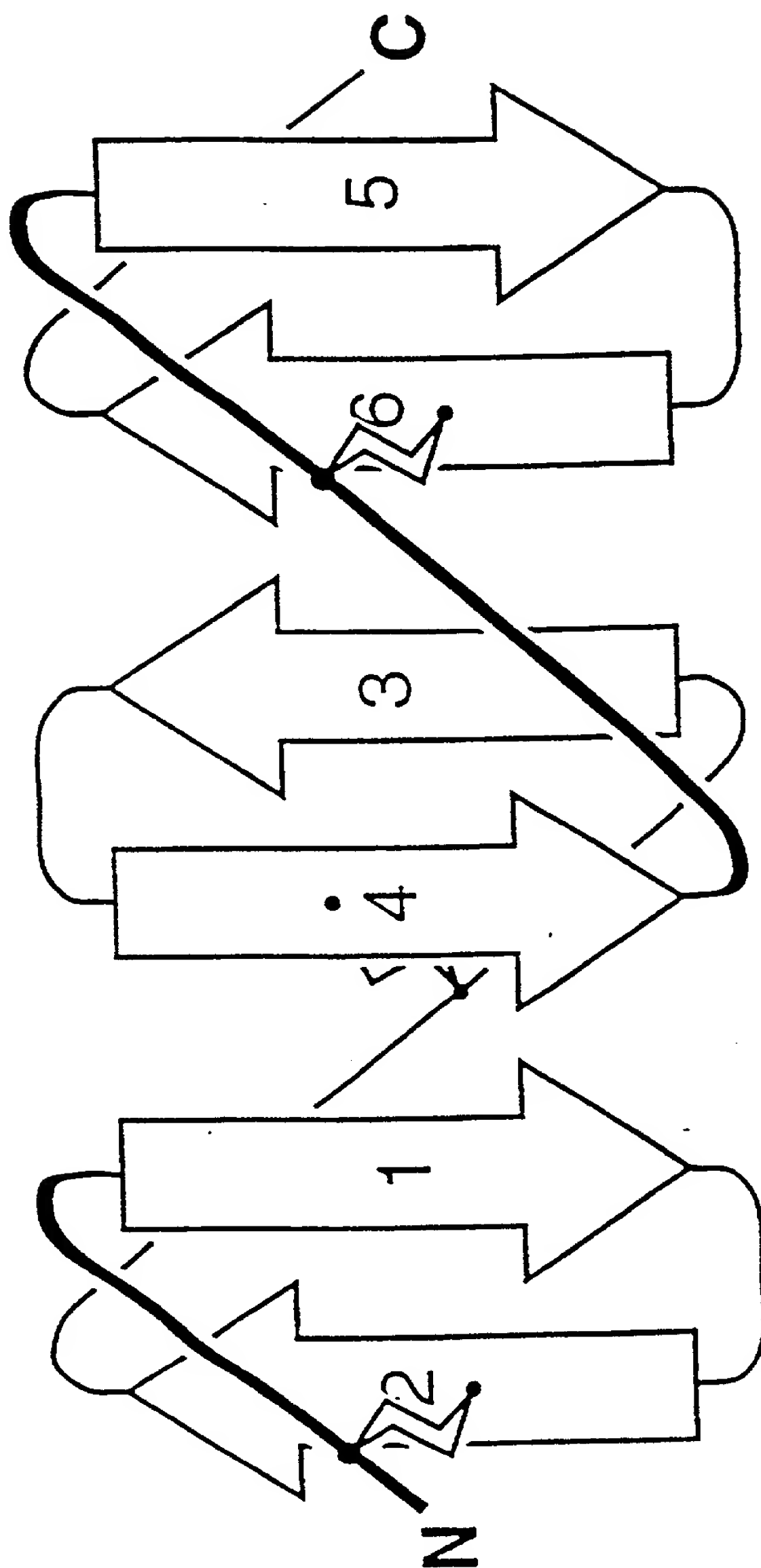
Figure 6

Figure 7

Figure 8

Figure 9: Sequence Alignment of hIGF-1R, hIR and hIRR ectodomains.

Derived by use of the PileUp program in the software package of the
Genetics Computer Group, 575 Science Drive, Madison, Wisconsin, USA.

```
Symbol Comparison table: GenRunData:PileUpPep.Cmp   CompCheck: 1254

                     GapWeight: 3.0
               GapLengthWeight: 0.1


Name: Higf1r            Len:  972  CheCk: 1781  Weight:  1.00
Name: Hir               Len:  972  CheCk: 2986  Weight:  1.00
Name: Hirr              Len:  972  CheCk: 9819  Weight:  1.00


                 *            *
Higf1r  .....EICGP GIDIRNDYQQ LKRLENCTVI EGYLHILLIS K..AEDYRSY  43
   Hir  HLYPGEVC.P GMDIRNNLTR LHELENCSVI EGHLQILLMF KTRPEDFRDL  49
  Hirr  ....MNVC.P SLDIRSEVAE LRQLENCSVV EGHLQILLMF TATGEDFRGL  45


Higf1r  RFPKLTVITE YLLLFRVAGL ESLGDLFPNL TVIRGWKLFY NYALVIFEMT  93
   Hir  SFPKLIMITD YLLLFRVYGL ESLKDLFPNL TVIRGSRLFF NYALVIFEMV  99
  Hirr  SFPRLTQVTD YLLLFRVYGL ESLRDLFPNL AVIRGTRLFL GYALVIFEMP  95

                                  *
Higf1r  NLKDIGLYNL RNITRGAIRI EKNADLCYLS TVDWSLILDA VSNNYIVGNK 143
   Hir  HLKELGLYNL MNITRGSVRI EKNNELCYLA TIDWSRILDS VEDNYIVLNK 149
  Hirr  HLRDVALPAL GAVLRGAVRV EKNQELCHLS TIDWGLLQPA PGANHIVGNK 145

            *   *            *         *        *      *   *
Higf1r  PPK.ECGDLC PGTMEEKPM. CEKTTINNEY NYRCWTTNRC QKMCPSTCGK 191
   Hir  DDNEECGDIC PGTAKGKTN. CPATVINGQF VERCWTHSHC QKVCPTICKS 198
  Hirr  LG.EECADVC PGVLGAAGEP CAKTTFSGHT DYRCWTSSHC QRVCPCPHG. 193

         *      * *   *     *         *   *          *      *
Higf1r  RACTENNECC HPECLGSCSA PDNDTACVAC RHYYYAGVCV PACPPNTYRF 241
   Hir  HGCTAEGLCC HSECLGNCSQ PDDPTKCVAC RNFYLDGRCV ETCPPPYYHF 248
  Hirr  MACTARGECC HTECLGGCSQ PEDPRACVAC RHLYFQGACL WACPPGTYQY 243

            *       *        *--------*          *    *
Higf1r  EGWRCVDRDF CANILSAES. ...SDSEGFV IHDGECMQEC PSGFIRNGSQ 287
   Hir  QDWRCVNESF CQDLHHKCKN SRRQGCHQYV IHNNKCIPEC PSGYTMNSSN 298
  Hirr  ESWRCVTAER CASLHSVPG. ....RASTFG IHQGSCLAQC PSGFTRNSS. 287

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Higf1r  SMYCIPCEGP CPKVCEEEKK TKTIDSVTSA QMLQGCTIFK GNLLINIRRG 337
   Hir  .LLCTPCLGP CPKVCHLLEG EKTIDSVTSA QELRGCTVIN GSLIINIRGG 347
  Hirr  SIFCHKCEGL CPKECKV..G TKTIDSIQAA QDLVGCTHVE GSLILNLRQG 335


Higf1r  NNIASELENF MGLIEVVTGY VKIRHSHALV SLSFLKNLRL ILGEEQLEGN  387
   Hir  NNLAAELEAN LGLIEEISGY LKIRRSYALV SLSFFRKLRL IRGETLEIGN  397
  Hirr  YNLEPQLQHS LGLVETITGF LKIKHSFALV SLGFFKNLKL IRGDAMVDGN  385

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Higf1r  YSFYVLDNQN LQQLWDWDHR NLTIKAGKMY FAFNPKLCVS EIYRMEEVTG  437
   Hir  YSFYALDNQN LRQLWDWSKH NLTITQGKLF FHYNPKLCLS EIHKMEEVSG  447
  Hirr  YTLYVLDNQN LQQLGSWVAA GLTIPVGKIY FAFNPRLCLE HIYRLEEVTG  435
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Higflr   TKGRQSKGDI NTRNNGERAS CESDV LHFTS TTTSKNRIII TWHRYRPPDY  487
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  Hirr   TRGRQNKAEI NPRTNGDRAA CQTRT LRFVS NVTEADRILL RWERYEPLEA  485
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Higflr   RDLISFTVYY KEAPFKNVTE YDGQDACGSN SWNMVDVDLP .....PNKDV  532
   Hir   RDLLGFMLFY KEAPYQNVTE FDGQDACGSN SWTVVDIDPP LRSNDPKSQN  547
  Hirr   RDLLSFIVYY KESPFQNATE HVGPDACGTQ SWNLLDVELP L.....SRTQ  530


Higflr   EPGILLHGLK PWTQYAVYVK AVTLTMVEND HIRGAKSEIL YIRTNASVPS  582
   Hir   HPGWLMRGLK PWTQYAIFVK TL.VTFSDER RTYGAKSDII YVQTDATNPS  596
  Hirr   EPGVTLASLK PWTQYAVFVR AITLTTEEDS PHQGAQSPIV YLRTLPAAPT  580


Higflr   IPLDVLSASN SSSQLIVKWN PPSLPNGNLS YYIVRWQRQP QDGYLYRHNY  632
   Hir   VPLDPISVSN SSSQIILKWK PPSDPNGNIT HYLVFWERQA EDSELFELDY  646
  Hirr   VPQDVISTSN SSSHLLVRWK PPTQRNGNLT YYLVLWQRLA EDGDLYLNDY  630

              *                         *    ** **   *
Higflr   CSKD.KIPIR KYADGTIDIE EVTENPKTEV CGGEKGPCCA C...PKTEAE  678
   Hir   CLKGLKLPSR TWS.PPFESE DSQKHNQSE. YEDSAGECCS C...PKTDSQ  691
  Hirr   CHRGLRLPTS N.NDPRFDGE DGDPEAEME. .....SDCCP CQHPPPGQVL  673

                              α------->< ------β
Higflr   KQAEKEEAEY RKVFENFLHN SIFVPRPERK RRDVMQVANT TMSSRSRNTT  728
   Hir   ILKELEESSF RKTFEDYLHN VVFVPRPSRK RRSLGDVGNV TVAVP...TV  738
  Hirr   PPLEAQEASF QKKFENFLHN AITIPISPWK VTSINKSPQR D.SGRHRRAA  722

                                                        *
Higflr   AA..DTYNIT DPEELETEYP FFESRVDNKE RTVISNLRPF TLYRIDIHSC  776
   Hir   AAFPNTSSTS VPTSPEEHRP F..EKVVNKE SLVISGLRHF TGYRIELQAC  786
  Hirr   GPLRLGGNSS DFEIQEDKVP ........RE RAVLSGLRHF TEYRIDIHAC  764

                  *
Higflr   NHEAEKLGCS ASNFVFARTM PAEGADDIPG PVTWEPRPEN SIFLKWPEPE  826
   Hir   NQDTPEERCS VAAYVSARTM PEAKADDIVG PVTHEIFENN VVHLMWQEPK  836
  Hirr   NHAAHTVGCS AATFVFARTM PHREADGIPG KVAWEASSKN SVLLRWLEPP  814

                              *               *
Higflr   NPNGLILMYE IKYGS.QVED QRECVSRQEY RKYGGAKLNR LNPGNYTARI  875
   Hir   EPNGLIVLYE VSYRRYGDEE LHLCVSRKHF ALERGCRLRG LSPGNYSVRI  886
  Hirr   DPNGLILKYE IKYRRLGEEA TVLCVSRLRY AKFGGVHLAL LPPGNYSARV  864


Higflr   QATSLSGNGS WTDPVFFYVQ AKTGYENFIH L                     906
   Hir   RATSLAGNGS WTEPTYFYVT DYLDVPSNIA K                     917
  Hirr   RATSLAGNGS WTDSVAFYIL GPEEEDAGGL H                     895
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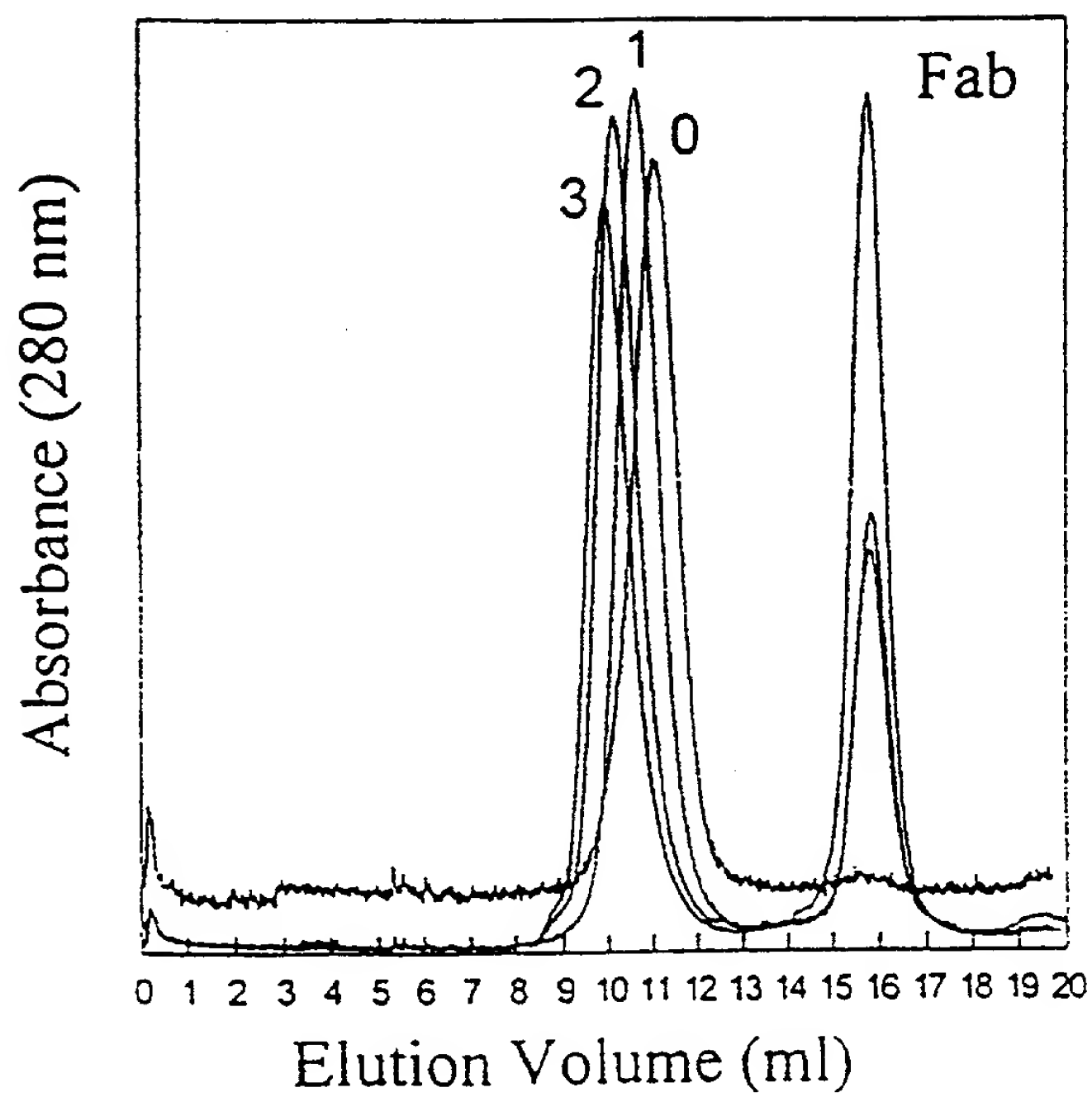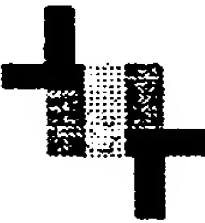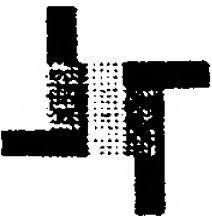
Figure 10

Schematic interpretations of EM images			
Sample	Projection along:		
	y axis	z axis	x axis
hIR			
hIR/ 83-7			
hIR/ 83-14			
hIR/ 18-44/83-14			
hIR/ 83-7/18-44			
hIR/ 83-7/83-14			

Figure 11

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Application(s))

Attorney's Docket Number
50179-081

As below named Inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

the specification of which:

☐　　　　is attached hereto.

☒　　　　was filed as United States application Serial No.　　09/555,275　　_____

　　　　　on　　May 26, 2000　　_____

　　　　　and was amended on　　_____　　(if applicable).

☒　　　　was filed as PCT international application Number　　PCT/AU98/00998　　_____

　　　　　on　　November 27, 1998　　_____

　　　　　and was amended under PCT Article 19 on　　_____　　(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or Section 365(b) of any foreign and/or international application(s) for patent or inventor's certificate or Section 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (If PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
AUSTRALIA	PP 0585	November 27, 1997	☒Yes ☐ No
AUSTRALIA	PP 2598	March 25, 1998	☒Yes ☐ No

I hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

PRIOR PROVISIONAL APPLICATION(S):

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned *(if any)*			
PCT/AU98/00998	November 27, 1998				

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 26,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg. No. P-46,578; Daniel Bucca, Reg. No. 42,368; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,469; Paul Devinsky, Reg. No. 28,553; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,139; John R. Fuisz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A. Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Lever, Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg. No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,669; Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,449; Arthur J. Steiner, Reg. No. 26,108; David L. Stewart, Reg. No. 37,578; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leonic D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Weisstuch, Reg. No. 41,557; Edward J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.

Send Correspondence to:	Direct Telephone Calls to: *(name and telephone number)*
McDERMOTT, WILL & EMERY 600 13th Street, N.W. Washington, D.C. 20005-3096	(202) 756-8000

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I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201: *John D Bentley*	Signature of Inventor 202: *L. Cos*	Signature of Inventor 203: *[signature]*
Date 1/8/01	Date 3/5/01.	Date August 1, 2001

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.		
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any)
PCT/AU98/00998	November 27, 1998	

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 26,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg. No. P-46,578; Daniel Bucca, Reg. No. 42,368; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,489; Paul Devinsky, Reg. No. 28,553; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,139; John R. Fuisz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A. Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Lever, Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg. No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,669; Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,449; Arthur J. Steiner, Reg. No. 26,106; David L. Stewart, Reg. No. 37,578; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leonid D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Weisstuch, Reg. No. 41,557; Edward J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.
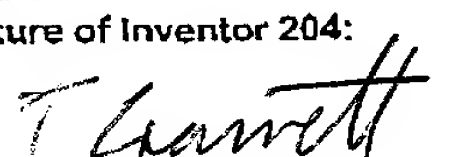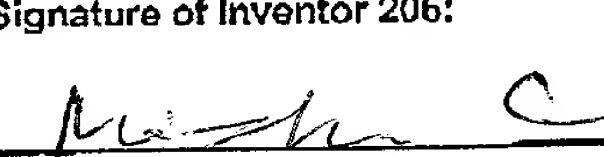
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I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 204: *T Garrett*	Signature of Inventor 205:	Signature of Inventor 206:
Date 1 Aug 01	Date 3/8/01	Date 1/8/01

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

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PCT/AU98/00998	November 27, 1998				

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8 — ᴄᴏ 208

Full Name of Inventor	Family Name	First Given Name	Second Given Name
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9 — ᴄᴏ 209

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; an further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuin thereon.

Signature of Inventor 207:	Signature of Inventor 208:	Signature of Inventor 209:
Date 3rd of Aug 200?	Date 2nd August 2001	Date 2 August 2001.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT International application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

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	Post Office Address	Post Office Address	City	State & Zip Code/Country
	Full Name of Inventor	Family Name	First Given Name	Second Given Name
212	Residence and Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country

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Signature of Inventor 210:	Signature of Inventor 211:	Signature of Inventor 212:
Paul Tulloch.		
Date 3 August 2001	Date	Date

PAUL TULLOCH — AS
THE LEGAL REPRESENTATIVE
FOR PETER A. TULLOCH.
INVENTOR N° 210

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

(Includes Reference to PCT International Application(s))

Attorney's Docket Number
50179-081

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

the specification of which:

☐   is attached hereto.

☒   was filed as United States application Serial No.   09/555,275

on   May 26, 2000

and was amended on _____ (if applicable).

☒   was filed as PCT international application Number   PCT/AU98/00998

on   November 27, 1998

and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or Section 365(b) of any foreign and/or international application(s) for patent or inventor's certificate or Section 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (If PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
AUSTRALIA	PP 0585	November 27, 1997	☒Yes ☐ No
AUSTRALIA	PP 2598	March 25, 1998	☒Yes ☐ No

I hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.
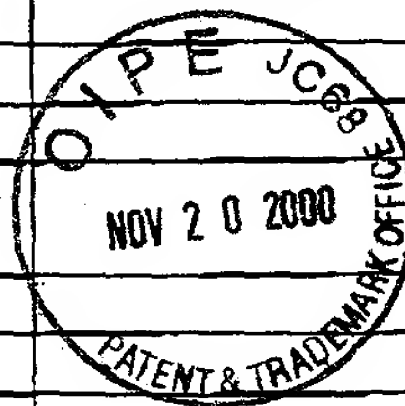
PRIOR PROVISIONAL APPLICATION(S):

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.				
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any)		
PCT/AU98/00998	November 27, 1998			

CIPE JC68 NOV 2 0 2000 PATENT & TRADEMARK OFFICE

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 25,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg No. P-46,578; Daniel Bucca, Reg. No. 42,366; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,489; Paul Devinsky, Reg. No. 28,553; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,135; John R. Fuisz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Lever Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg. No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,56 Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,44 Arthur J. Steiner, Reg. No. 26,106; David L. Stewart, Reg. No. 37,578; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leor D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Weisstuch, Reg. No. 41,557; Edwa J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.

Send Correspondence to:	Direct Telephone Calls to: (name and telephone number)
McDERMOTT, WILL & EMERY 600 13th Street, N.W. Washington, D.C. 20005-3096	(202) 756-8000

	Full Name of Inventor (LEGAL REPRESENTATIVE)	Family Name Tulloch	First Given Name Paul	Second Given Name Alexander
210	Residence and Citizenship	City Denmark AUX	State or Foreign Country Western Australia	Country of Citizenship Australia
	Post Office Address	Post Office Address 9 Braidwood Elbow	City Denmark	State & Zip Code/Country Western Australia 6333
	Full Name of Inventor	Family Name	First Given Name	Second Given Name
211	Residence and Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
	Full Name of Inventor	Family Name	First Given Name	Second Given Name
212	Residence and Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true: further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or bot under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent iss thereon.

Signature of Inventor 210: *[signature]*	Signature of Inventor 211:	Signature of Inventor 212:
Date 20/10/2000	Date	Date

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §(c) of any PCT International application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any)			
PCT/AU98/00998	November 27, 1998				

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business at the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 26,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg No. P-46,578; Daniel Bucca, Reg. No. 42,368; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,489; Paul Devinsky, Reg. No. 28,553; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,139; John R. Fuisz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Leve Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,66; Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,44; Arthur J. Steiner, Reg. No. 26,106; David L. Stewart, Reg. No. 37,579; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leon. D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Waisstuch, Reg. No. 41,557; Edwar J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.

Send Correspondence to:	Direct Telephone Calls to:
McDERMOTT, WILL & EMERY 600 13th Street, N.W. Washington, D.C. 20005-3096	(name and telephone number) (202) 756-8000

201	Full Name of Inventor	Family Name Bentley	First Given Name John	Second Given Name David
	Residence and Citizenship	City Macedon AUX	State or Foreign Country Victoria	Country of Citizenship Australia
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202	Full Name of Inventor	Family Name Cosgrove	First Given Name Leah	Second Given Name Jane
	Residence and Citizenship	City Somerton Park AUX	State or Foreign Country South Australia	Country of Citizenship Australia
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203	Full Name of Inventor	Family Name Frenkel	First Given Name Maurice	Second Given Name John
	Residence and Citizenship	City South Caulfield AUX	State or Foreign Country Victoria	Country of Citizenship Australia
	Post Office Address	Post Office Address 232 Ellington Street	City South Caulfield	State & Zip Code/Country Victoria 3162

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; a further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issu thereon.

Signature of Inventor 201: John D Bentley	Signature of Inventor 202: L. Cq	Signature of Inventor 203: Frenkel
Date 9 OCT 2000	Date 13 October 2000	Date 10 October 2000

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any).			
PCT/AU98/00998	November 27, 1998				

(Stamp: OIPE JC68 NOV 20 2000 PATENT & TRADEMARK OFFICE)

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 26,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg. No. P-46,578; Daniel Bucca, Reg. No. 42,368; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,489; Paul Devinsky, Reg. No. 28,553; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,139; John R. Fulsz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A. Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Lever, Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg. No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,669; Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,449; Arthur J. Steiner, Reg. No. 26,106; David L. Stewart, Reg. No. 37,578; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leonid D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Weisstuch, Reg. No. 41,557; Edward J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.

Send Correspondence to:	Direct Telephone Calls to:
McDERMOTT, WILL & EMERY 600 13th Street, N.W. Washington, D.C. 20005-3096	(name and telephone number) (202) 756-8000

Full Name of Inventor	Family Name Garrett	First Given Name Thomas	Second Given Name Peter John
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Full Name of Inventor	Family Name Lou	First Given Name Meizhen	Second Given Name
Residence and Citizenship	City Scoresby AUX	State or Foreign Country Victoria	Country of Citizenship Australian
Post Office Address	Post Office Address 10 Roma Street	City Scoresby	State & Zip Code/Country Victoria 3179

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 204:	Signature of Inventor 205:	Signature of Inventor 206:
Garrett	*Lar*	*Meizhen Lou*
Date 9 Oct 2000	Date 9 October 2000	Date 9 oct. 2000

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §(c) of any PCT International application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S.				
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any)		
PCT/AU98/00998	November 27, 1998			

[Stamp: OIPE JC68 NOV 20 2000 PATENT & TRADEMARK OFFICE]

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Becker, Reg. No. 26,527; John G. Bisbikis, Reg. No. 37,095; Christopher D. Bright, Reg. No. P-46,578; Daniel Bucca, Reg. No. 42,368; Kenneth L. Cage, Reg. No. 26,151; Stephen C. Carlson, Reg. No. 39,929; Jennifer Chen, Reg. No. 42,404; Bernard P. Codd, Reg. No. 46,429; Thomas A. Corrado, Reg. No. 42,439; Lawerence T. Cullen, Reg. No. 44,489; Paul Devinsky, Reg. No. 28,559; Margaret M. Duncan, Reg. No. 30,879; Ramyar M. Farid, Reg. No. P-46,692; Brian E. Ferguson, Reg. No. 36,801; Michael E. Fogarty, Reg. No. 36,136; John R. Fuisz, Reg. No. 37,327; Willem F. Gadiano, Reg. No. 37,136; Keith E. George, Reg. No. 34,111; Matthew V. Grumbling, Reg. No. 44,427; John A. Hankins, Reg. No. 32,029; Joseph Hyosuk Kim, Reg. No. 41,425; Eric J. Kraus, Reg. No. 36,190; Catherine Krupka, Reg. No. 46,227; Jack Q. Leve, Reg. No. 28,149; Raphael V. Lupo, Reg. No. 28,363; Michael A. Messina, Reg. No. 33,424; Dawn L. Palmer, Reg. No. 41,238; Joseph H. Paquin, Jr., Reg. No. 31,647; Scott D. Paul, Reg. No. 42,984; William D. Pegg, Reg. No. 42,988; Robert L. Price, Reg. No. 22,685; Thomas D. Robbins, Reg. No. 43,669; Gene Z. Rubinson, Reg. No. 33,351; Joy Ann G. Serauskas, Reg. No. 27,952; Daniel H. Sherr, Reg. No. P-46,425; David A. Spenard, Reg. No. 37,441; Arthur J. Steiner, Reg. No. 26,106; David L. Stewart, Reg. No. 37,578; Wesley Strickland, Reg. No. 44,363; Michael D. Switzer, Reg. No. 39,552; Leon D. Thenor, Reg. No. 39,397; Daniel S. Trainor, Reg. No. 43,959; Cameron K. Weiffenbach, Reg. No. 44,488; Aaron Weisstuch, Reg. No. 41,557; Edward J. Wise, Reg. No. 34,523; Alexander V. Yampolsky, Reg. No. 36,324; and Robert W. Zelnick, Reg. No. 36,976, all of McDermott, Will & Emery.

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McDERMOTT, WILL & EMERY 600 13th Street, N.W. Washington, D.C. 20005-3096	(name and telephone number) (202) 756-8000

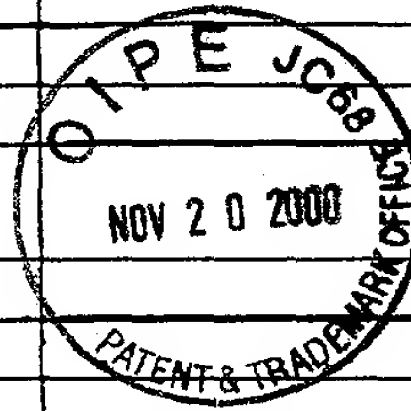|	Full Name of Inventor	Family Name	First Given Name	Second Given Name
207		Lovrecz	George	Oscar
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208	Full Name of Inventor	Family Name McKern	First Given Name Neil	Second Given Name Moreton
	Residence and Citizenship	City Lilydale AUX	State or Foreign Country Victoria	Country of Citizenship Australia
	Post Office Address	Post Office Address Como Road	City Lilydale	State & Zip Code/Country Victoria 3170
209	Full Name of Inventor	Family Name Ward	First Given Name Colin	Second Given Name Wesley
	Residence and Citizenship	City Carlton AUX	State or Foreign Country Victoria	Country of Citizenship Australia
	Post Office Address	Post Office Address 903 Rathdowne Street	City Carlton	State & Zip Code/Country Victoria 3053

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature of Inventor 207:	Signature of Inventor 208:	Signature of Inventor 209:
[signature]	*[signature]*	*[signature]*
Date 9th October 2000	Date 9th October 2000	Date 9 October 2000

SEQUENCE LISTING

<110> Commonwealth Scientific and Industrial Research Organisation

<120> Method of Designing Agonists and Antagonists to IGF Receptor

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<140> 09/555,275
<141> 2000-05-26

<150> PCT/AU98/00998
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Leu Ile Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu
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Thr Val Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu
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Ser Leu Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys
65   70   75   80

Leu Phe Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys
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Asp Ile Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg
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        35                  40                  45

Leu Ser Phe Pro Lys Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe
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Arg Val Tyr Gly Leu Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr
65                  70                  75                  80

Val Ile Arg Gly Ser Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe
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Glu Met Val His Leu Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile
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Val Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu
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Gln Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala
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Val Leu Ser Asn Tyr Asp Ala Asn Lys Thr Gly Leu Xaa Xaa Lys Pro
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<223>  Protein sequence known but not provided in Figure 6a


<220>
<221>  MISC_FEATURE
<222>  (44)..(50)
<223>  Protein sequence known but not provided in Figure 6a


<400>  4

Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Xaa Xaa Xaa Xaa Xaa Xaa
1               5               10                  15


Xaa Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser
            20                  25                  30


Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Xaa Xaa Xaa Xaa Xaa
            35                  40                  45


Xaa Xaa Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val
    50                  55                  60


Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg
65                  70                  75                  80


Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr
            85                  90                  95


Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr
            100                 105                 110
```

Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile
        115   120   125

Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys
        130   135   140

Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg
145   150   155   160

Gly Glu Asn Ser Cys Lys Ala
                165

<210>   5
<211>   161
<212>   PRT
<213>   Homo sapiens

<400>   5

Lys Val Cys His Leu Leu Glu Gly Glu Lys Thr Ile Asp Ser Val Thr
1   5   10   15

Ser Ala Gln Glu Leu Arg Gly Cys Thr Val Ile Asn Gly Ser Leu Ile
                20   25   30

Ile Asn Ile Arg Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu Ala Asn
            35   40   45

Leu Gly Leu Ile Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser
        50   55   60

Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg
65   70   75   80

Gly Glu Thr Leu Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn
                85   90   95

Gln Asn Leu Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Ile
            100   105   110

Thr Gln Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser
        115   120   125

Glu Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu
        130   135   140

Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Lys Ala Ser Cys Glu
145   150   155   160

Asn

<210> 6
<211> 161
<212> PRT
<213> Homo sapiens

<400> 6

Lys Val Cys Glu Glu Glu Lys Lys Thr Lys Thr Ile Asp Ser Val Thr
1   5   10   15

Ser Ala Gln Met Leu Gln Gly Cys Thr Ile Phe Lys Gly Asn Leu Leu
            20   25   30

Ile Asn Ile Arg Arg Gly Asn Asn Ile Ala Ser Glu Leu Glu Asn Phe
        35   40   45

Met Gly Leu Ile Glu Val Val Thr Gly Tyr Val Lys Ile Arg His Ser
    50   55   60

His Ala Leu Val Ser Leu Ser Phe Leu Lys Asn Leu Arg Leu Ile Leu
65   70   75   80

Gly Glu Glu Gln Leu Glu Gly Asn Tyr Ser Phe Tyr Val Leu Asp Asn
            85   90   95

Gln Asn Leu Gln Gln Leu Trp Asp Trp Asp His Arg Asn Leu Thr Ile
        100   105   110

Lys Ala Gly Lys Met Tyr Phe Ala Phe Asn Pro Lys Leu Cys Val Ser
        115   120   125

Glu Ile Tyr Arg Met Glu Glu Val Thr Gly Thr Lys Gly Arg Gln Ser
    130   135   140

Lys Gly Asp Ile Asn Thr Arg Asn Asn Gly Glu Arg Ala Ser Cys Glu
145   150   155   160

Ser

<210>   7
<211>   150
<212>   PRT
<213>   Homo sapiens

<400>   7

Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys Glu Lys Thr
1   5   10   15

Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr Asn Arg Cys
                20   25   30

Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys Thr Glu Asn
            35   40   45

Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser Ala Pro Asp
        50   55   60

Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr Ala Gly Val
65   70   75   80

Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu Gly Trp Arg
                85   90   95

Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala Glu Ser Ser
                100   105   110

Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met Gln Glu Cys
            115   120   125

Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr Cys Ile Pro
        130   135   140

Cys Glu Gly Pro Cys Pro
145   150

<210>   8
<211>   153
<212>   PRT
<213>   Homo sapiens

<400>   8

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Asp Ile Cys Pro Gly Thr Ala Lys Gly Lys Thr Asn Cys Pro Ala Thr
1                   5                   10                  15

Val Ile Asn Gly Gln Phe Val Glu Arg Cys Trp Thr His Ser His Cys
                20                  25                  30

Gln Lys Val Cys Pro Thr Ile Cys Lys Ser His Gly Cys Thr Ala Glu
            35                  40                  45

Gly Leu Cys Cys His Ser Glu Cys Leu Gly Asn Cys Ser Gln Pro Asp
        50                  55                  60

Asp Pro Thr Lys Cys Val Ala Cys Arg Asn Phe Tyr Leu Asp Gly Arg
65                  70                  75                  80

Cys Val Glu Thr Cys Pro Pro Pro Tyr Tyr His Phe Gln Asp Trp Arg
            85                  90                  95

Cys Val Asn Phe Ser Phe Cys Gln Asp Leu His His Lys Cys Lys Asn
            100                 105                 110

Ser Arg Arg Gln Gly Cys His Gln Tyr Val Ile His Asn Asn Lys Cys
        115                 120                 125

Ile Pro Glu Cys Pro Ser Gly Tyr Thr Met Asn Ser Ser Asn Leu Leu
    130                 135                 140

Cys Thr Pro Cys Leu Gly Pro Cys Pro
145                 150
```

<210> 9
<211> 146
<212> PRT
<213> Homo sapiens

<400> 9

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Lys Cys Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu
1                   5                   10                  15

Glu Asn Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser
                20                  25                  30

Gly Arg Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys
```

Ala Ala Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg
　　　50　　　　　　　　　　　55　　　　　　　　　60

Lys Phe Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met
65　　　　　　　　　　　70　　　　　　　　　75　　　　　　　　　80

Leu Tyr Asn Pro Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys
　　　　　　　　　85　　　　　　　　　90　　　　　　　　　95

Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val
　　　　　　　100　　　　　　　　　105　　　　　　　　　110

Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr
　　　　　115　　　　　　　　　120　　　　　　　　　125

Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro
　　　130　　　　　　　　　135　　　　　　　　　140

Cys Arg
145

<210> 10
<211> 142
<212> PRT
<213> Homo sapiens

<400> 10

Gln Val Cys His Ala Leu Cys Ser Pro Gly Cys Trp Gly Pro Glu
1　　　　　　　　5　　　　　　　　10　　　　　　　　15

Pro Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys
　　　　　　　20　　　　　　　　25　　　　　　　　30

Val Asp Lys Cys Lys Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu
　　　　　35　　　　　　　　　40　　　　　　　　　45

Asn Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met
　　　50　　　　　　　　　55　　　　　　　　　60

Asn Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala
65　　　　　　　　　70　　　　　　　　　75　　　　　　　　　80

His Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val
                85   90   95

Met Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His
               100   105   110

Val Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro
        115   120   125

Gly Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser
    130   135   140

<210>   11
<211>   906
<212>   PRT
<213>   Homo sapiens

<400>   11

Glu Ile Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu
1   5   10   15

Lys Arg Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu
             20   25   30

Leu Ile Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu
            35   40   45

Thr Val Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu
    50   55   60

Ser Leu Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys
65   70   75   80

Leu Phe Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys
                85   90   95

Asp Ile Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg
               100   105   110

Ile Glu Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser
        115   120   125

Leu Ile Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro

Pro Lys Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro
145   150   155   160

Met Cys Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp
                  165   170   175

Thr Thr Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg
              180   185   190

Ala Cys Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser
              195   200   205

Cys Ser Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr
          210   215   220

Tyr Tyr Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg
225   230   235   240

Phe Glu Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu
              245   250   255

Ser Ala Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu
              260   265   270

Cys Met Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser
          275   280   285

Met Tyr Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu
          290   295   300

Glu Lys Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu
305   310   315   320

Gln Gly Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg
              325   330   335

Gly Asn Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu
          340   345   350

Val Val Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser
          355   360   365

```
Leu Ser Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu
    370             375             380

Glu Gly Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln
385             390             395             400

Leu Trp Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met
            405             410             415

Tyr Phe Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met
        420             425             430

Glu Glu Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn
        435             440             445

Thr Arg Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His
    450             455             460

Phe Thr Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His
465             470             475             480

Arg Tyr Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr
            485             490             495

Tyr Lys Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp
        500             505             510

Ala Cys Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro
        515             520             525

Asn Lys Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp
    530             535             540

Thr Gln Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu
545             550             555             560

Asn Asp His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr
            565             570             575

Asn Ala Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn
        580             585             590
```

```
Ser Ser Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn
        595             600             605

Gly Asn Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp
        610             615             620

Gly Tyr Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile
625             630             635             640

Arg Lys Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn
                645             650             655

Pro Lys Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys
                660             665             670

Pro Lys Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr
        675             680             685

Arg Lys Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg
        690             695             700

Pro Glu Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met
705             710             715             720

Ser Ser Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr
                725             730             735

Asp Pro Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val
                740             745             750

Asp Asn Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu
        755             760             765

Tyr Arg Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly
        770             775             780

Cys Ser Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly
785             790             795             800

Ala Asp Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn
                805             810             815
```

Ser Ile Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile
            820   825   830

Leu Met Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu
            835   840   845

Cys Val Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn
            850   855   860

Arg Leu Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu
865   870   875   880

Ser Gly Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala
            885   890   895

Lys Thr Gly Tyr Glu Asn Phe Ile His Leu
            900   905

<210>   12
<211>   916
<212>   PRT
<213>   Homo sapiens

<400>   12

His Leu Tyr Pro Gly Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn
1   5   10   15

Leu Thr Arg Leu His Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His
            20   25   30

Leu Gln Ile Leu Leu Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp
            35   40   45

Leu Ser Phe Pro Lys Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe
            50   55   60

Arg Val Tyr Gly Leu Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr
65   70   75   80

Val Ile Arg Gly Ser Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe
            85   90   95

Glu Met Val His Leu Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile
            100   105   110

Thr Arg Gly Ser Val Arg Ile Glu Lys Asn Asn Glu Leu Cys Tyr Leu
        115   120   125

Ala Thr Ile Asp Trp Ser Arg Ile Leu Asp Ser Val Glu Asp Asn Tyr
        130   135   140

Ile Val Leu Asn Asp Asp Asn Glu Glu Cys Gly Asp Ile Cys Pro Gly
145   150   155   160

Thr Ala Lys Gly Lys Thr Asn Cys Pro Ala Thr Val Ile Asn Gly Gln
                165   170   175

Phe Val Glu Arg Cys Trp Thr His Ser His Cys Gln Lys Val Cys Pro
                180   185   190

Thr Ile Cys Lys Ser His Gly Cys Thr Ala Glu Gly Leu Cys Cys His
        195   200   205

Ser Glu Cys Leu Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys
        210   215   220

Val Ala Cys Arg Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys
225   230   235   240

Pro Pro Pro Tyr Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser
                245   250   255

Phe Cys Gln Asp Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly
                260   265   270

Cys His Gln Tyr Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys Pro
        275   280   285

Ser Gly Tyr Thr Met Asn Ser Ser Asn Leu Leu Cys Thr Pro Cys Leu
        290   295   300

Gly Pro Cys Pro Lys Val Cys His Leu Leu Glu Gly Glu Lys Thr Ile
305   310   315   320

Asp Ser Val Thr Ser Ala Gln Glu Leu Arg Gly Cys Thr Val Ile Asn
                325   330   335

```
Gly Ser Leu Ile Ile Asn Ile Arg Gly Gly Asn Asn Leu Ala Ala Glu
        340             345             350

Leu Glu Ala Asn Leu Gly Leu Ile Glu Glu Ile Ser Gly Tyr Leu Lys
        355             360             365

Ile Arg Arg Ser Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu
        370             375             380

Arg Leu Ile Arg Gly Glu Thr Leu Glu Ile Gly Asn Tyr Ser Phe Tyr
385             390             395             400

Ala Leu Asp Asn Gln Asn Leu Arg Gln Leu Trp Asp Trp Ser Lys His
            405             410             415

Asn Leu Thr Ile Thr Gln Gly Lys Leu Phe Phe His Tyr Asn Pro Lys
        420             425             430

Leu Cys Leu Ser Glu Ile His Lys Met Glu Glu Val Ser Gly Thr Lys
        435             440             445

Gly Arg Gln Glu Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Gln
        450             455             460

Ala Ser Cys Glu Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser
465             470             475             480

Phe Asp Lys Ile Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe
            485             490             495

Arg Asp Leu Leu Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln
        500             505             510

Asn Val Thr Glu Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser Trp
        515             520             525

Thr Val Val Asp Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro Lys Ser
        530             535             540

Gln Asn His Pro Gly Trp Leu Met Arg Gly Leu Lys Pro Trp Thr Gln
545             550             555             560
```

Tyr Ala Ile Phe Val Lys Thr Leu Val Thr Phe Ser Asp Glu Arg Arg
                    565   570   575

Thr Tyr Gly Ala Lys Ser Asp Ile Ile Tyr Val Gln Thr Asp Ala Thr
                580   585   590

Asn Pro Ser Val Pro Leu Asp Pro Ile Ser Val Ser Asn Ser Ser Ser
                595   600   605

Gln Ile Ile Leu Lys Trp Lys Pro Pro Ser Asp Pro Asn Gly Asn Ile
        610   615   620

Thr His Tyr Leu Val Phe Trp Glu Arg Gln Ala Glu Asp Ser Glu Leu
625   630   635   640

Phe Glu Leu Asp Tyr Cys Leu Lys Gly Leu Lys Leu Pro Ser Arg Thr
                645   650   655

Trp Ser Pro Pro Phe Glu Ser Glu Asp Ser Gln Lys His Asn Gln Ser
                660   665   670

Glu Tyr Glu Asp Ser Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp
            675   680   685

Ser Gln Ile Leu Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe
        690   695   700

Glu Asp Tyr Leu His Asn Val Val Phe Val Pro Arg Pro Ser Arg Lys
705   710   715   720

Arg Arg Ser Leu Gly Asp Val Gly Asn Val Thr Val Ala Val Pro Thr
                725   730   735

Val Ala Ala Phe Pro Asn Thr Ser Ser Thr Ser Val Pro Thr Ser Pro
                740   745   750

Glu Glu His Arg Pro Phe Glu Lys Val Val Asn Lys Glu Ser Leu Val
                755   760   765

Ile Ser Gly Leu Arg His Phe Thr Gly Tyr Arg Ile Glu Leu Gln Ala
        770   775   780

Cys Asn Gln Asp Thr Pro Glu Glu Arg Cys Ser Val Ala Ala Tyr Val

Ser Ala Arg Thr Met Pro Glu Ala Lys Ala Asp Asp Ile Val Gly Pro
            805   810   815

Val Thr His Glu Ile Phe Glu Asn Asn Val Val His Leu Met Trp Gln
            820   825   830

Glu Pro Lys Glu Pro Asn Gly Leu Ile Val Leu Tyr Glu Val Ser Tyr
            835   840   845

Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys Val Ser Arg Lys His
        850   855   860

Phe Ala Leu Glu Arg Gly Cys Arg Leu Arg Gly Leu Ser Pro Gly Asn
865   870   875   880

Tyr Ser Val Arg Ile Arg Ala Thr Ser Leu Ala Gly Asn Gly Ser Trp
            885   890   895

Thr Glu Pro Thr Tyr Phe Tyr Val Thr Asp Tyr Leu Asp Val Pro Ser
            900   905   910

Asn Ile Ala Lys
            915

<210>   13
<211>   895
<212>   PRT
<213>   Homo sapiens

<400>   13

Met Asn Val Cys Pro Ser Leu Asp Ile Arg Ser Glu Val Ala Glu Leu
1   5   10   15

Arg Gln Leu Glu Asn Cys Ser Val Val Glu Gly His Leu Gln Ile Leu
            20   25   30

Leu Met Phe Thr Ala Thr Gly Glu Asp Phe Arg Gly Leu Ser Phe Pro
            35   40   45

Arg Leu Thr Gln Val Thr Asp Tyr Leu Leu Leu Phe Arg Val Tyr Gly
        50   55   60

```
Leu Glu Ser Leu Arg Asp Leu Phe Pro Asn Leu Ala Val Ile Arg Gly
65              70              75                  80

Thr Arg Leu Phe Leu Gly Tyr Ala Leu Val Ile Phe Glu Met Pro His
                85              90                  95

Leu Arg Asp Val Ala Leu Pro Ala Leu Gly Ala Val Leu Arg Gly Ala
            100             105             110

Val Arg Val Glu Lys Asn Gln Glu Leu Cys His Leu Ser Thr Ile Asp
            115             120             125

Trp Gly Leu Leu Gln Pro Ala Pro Gly Ala Asn His Ile Val Gly Asn
        130             135             140

Lys Leu Gly Glu Glu Cys Ala Asp Val Cys Pro Gly Val Leu Gly Ala
145             150             155             160

Ala Gly Glu Pro Cys Ala Lys Thr Thr Phe Ser Gly His Thr Asp Tyr
            165             170             175

Arg Cys Trp Thr Ser Ser His Cys Gln Arg Val Cys Pro Cys Pro His
            180             185             190

Gly Met Ala Cys Thr Ala Arg Gly Glu Cys Cys His Thr Glu Cys Leu
        195             200             205

Gly Gly Cys Ser Gln Pro Glu Asp Pro Arg Ala Cys Val Ala Cys Arg
    210             215             220

His Leu Tyr Phe Gln Gly Ala Cys Leu Trp Ala Cys Pro Pro Gly Thr
225             230             235             240

Tyr Gln Tyr Glu Ser Trp Arg Cys Val Thr Ala Glu Arg Cys Ala Ser
            245             250             255

Leu His Ser Val Pro Gly Arg Ala Ser Thr Phe Gly Ile His Gln Gly
            260             265             270

Ser Cys Leu Ala Gln Cys Pro Ser Gly Phe Thr Arg Asn Ser Ser Ser
    275             280             285
```

```
Ile Phe Cys His Lys Cys Glu Gly Leu Cys Pro Lys Glu Cys Lys Val
    290                 295             300

Gly Thr Lys Thr Ile Asp Ser Ile Gln Ala Ala Gln Asp Leu Val Gly
305             310             315                 320

Cys Thr His Val Glu Gly Ser Leu Ile Leu Asn Leu Arg Gln Gly Tyr
                325             330                 335

Asn Leu Glu Pro Gln Leu Gln His Ser Leu Gly Leu Val Glu Thr Ile
            340             345                 350

Thr Gly Phe Leu Lys Ile Lys His Ser Phe Ala Leu Val Ser Leu Gly
        355             360                 365

Phe Phe Lys Asn Leu Lys Leu Ile Arg Gly Asp Ala Met Val Asp Gly
    370             375             380

Asn Tyr Thr Leu Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Gly
385             390             395                 400

Ser Trp Val Ala Ala Gly Leu Thr Ile Pro Val Gly Lys Ile Tyr Phe
            405             410             415

Ala Phe Asn Pro Arg Leu Cys Leu Glu His Ile Tyr Arg Leu Glu Glu
            420             425             430

Val Thr Gly Thr Arg Gly Arg Gln Asn Lys Ala Glu Ile Asn Pro Arg
        435             440             445

Thr Asn Gly Asp Arg Ala Ala Cys Gln Thr Arg Thr Leu Arg Phe Val
        450             455             460

Ser Asn Val Thr Glu Ala Asp Arg Ile Leu Leu Arg Trp Glu Arg Tyr
465             470             475                 480

Glu Pro Leu Glu Ala Arg Asp Leu Leu Ser Phe Ile Val Tyr Tyr Lys
            485             490             495

Glu Ser Pro Phe Gln Asn Ala Thr Glu His Val Gly Pro Asp Ala Cys
            500             505             510

Gly Thr Gln Ser Trp Asn Leu Leu Asp Val Glu Leu Pro Leu Ser Arg
```

Thr Gln Glu Pro Gly Val Thr Leu Ala Ser Leu Lys Pro Trp Thr Gln
    530   535   540

Tyr Ala Val Phe Val Arg Ala Ile Thr Leu Thr Thr Glu Glu Asp Ser
545   550   555   560

Pro His Gln Gly Ala Gln Ser Pro Ile Val Tyr Leu Arg Thr Leu Pro
            565   570   575

Ala Ala Pro Thr Val Pro Gln Asp Val Ile Ser Thr Ser Asn Ser Ser
            580   585   590

Ser His Leu Leu Val Arg Trp Lys Pro Pro Thr Gln Arg Asn Gly Asn
        595   600   605

Leu Thr Tyr Tyr Leu Val Leu Trp Gln Arg Leu Ala Glu Asp Gly Asp
    610   615   620

Leu Tyr Leu Asn Asp Tyr Cys His Arg Gly Leu Arg Leu Pro Thr Ser
625   630   635   640

Asn Asn Asp Pro Arg Phe Asp Gly Glu Asp Gly Asp Pro Glu Ala Glu
            645   650   655

Met Glu Ser Asp Cys Cys Pro Cys Gln His Pro Pro Pro Gly Gln Val
            660   665   670

Leu Pro Pro Leu Glu Ala Gln Glu Ala Ser Phe Gln Lys Lys Phe Glu
    675   680   685

Asn Phe Leu His Asn Ala Ile Thr Ile Pro Ile Ser Pro Trp Lys Val
    690   695   700

Thr Ser Ile Asn Lys Ser Pro Gln Arg Asp Ser Gly Arg His Arg Arg
705   710   715   720

Ala Ala Gly Pro Leu Arg Leu Gly Gly Asn Ser Ser Asp Phe Glu Ile
            725   730   735

Gln Glu Asp Lys Val Pro Arg Glu Arg Ala Val Leu Ser Gly Leu Arg
            740   745   750

His Phe Thr Glu Tyr Arg Ile Asp Ile His Ala Cys Asn His Ala Ala
        755   760   765

His Thr Val Gly Cys Ser Ala Ala Thr Phe Val Phe Ala Arg Thr Met
        770   775   780

Pro His Arg Glu Ala Asp Gly Ile Pro Gly Lys Val Ala Trp Glu Ala
785   790   795   800

Ser Ser Lys Asn Ser Val Leu Leu Arg Trp Leu Glu Pro Pro Asp Pro
                805   810   815

Asn Gly Leu Ile Leu Lys Tyr Glu Ile Lys Tyr Arg Arg Leu Gly Glu
                820   825   830

Glu Ala Thr Val Leu Cys Val Ser Arg Leu Arg Tyr Ala Lys Phe Gly
        835   840   845

Gly Val His Leu Ala Leu Leu Pro Pro Gly Asn Tyr Ser Ala Arg Val
        850   855   860

Arg Ala Thr Ser Leu Ala Gly Asn Gly Ser Trp Thr Asp Ser Val Ala
865   870   875   880

Phe Tyr Ile Leu Gly Pro Glu Glu Glu Asp Ala Gly Gly Leu His
                885   890   895

<210> 14
<211> 68
<212> DNA
<213> Artificial sequence

<220>
<223> Unknown Organism

<400> 14
gacgtcgacg atgacgataa ggaacaaaaa ctcatctcag aagaggatct gaattagaat   60

tcgacgtc   68

<210> 15
<211> 18
<212> PRT
<213> Homo sapiens

<400> 15

Asp Val Asp Asp Asp Asp Lys Glu Gln Lys Leu Ile Ser Glu Glu Asp
1   5   10   15

Leu Asn